MONOGRAPHS ON EXPERIMENTAL BIOLOGY

THE BIOLOGY OF DEATH

BY

RAYMOND PEARL
THE JOHNS HOPKINS UNIVERSITY

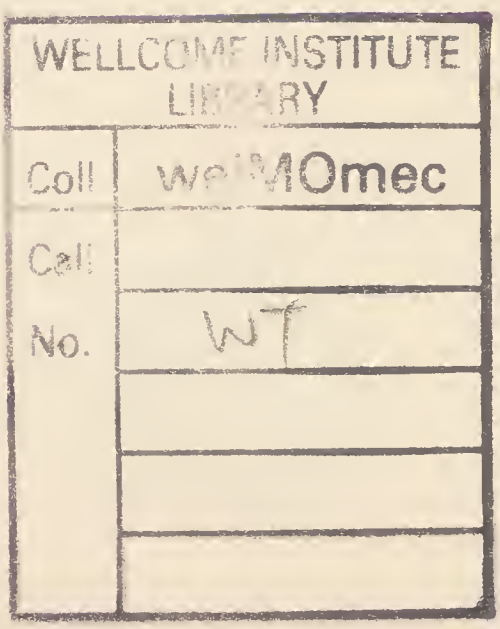
MONOGRAPHS ON EXPERIMENTAL BIOLOGY

THE BIOLOGY OF DEATH

Being a Series of Lectures Delivered at the Lowell Institute in Boston in December 1920

BY
RAYMOND PEARL
THE JOHNS HOPKINS UNIVERSITY

PHILADELPHIA AND LONDON
J. B. LIPPINCOTT COMPANY



PRINTED BY J. B. LIPPINCOTT COMPANY
AT THE WASHINGTON SQUARE PRESS
PHILADELPHIA, U. S. A.

TO

MY WISEST COUNSELLOR

M. D. P.

EDITOR'S ANNOUNCEMENT

The rapidly increasing specialization makes it impossible for one author to cover satisfactorily the whole field of modern Biology. This situation, which exists in all the sciences, has induced English authors to issue series of monographs in Biochemistry, Physiology, and Physics. A number of American biologists have decided to provide the same opportunity for the study of Experimental Biology.

Biology, which not long ago was purely descriptive and speculative, has begun to adopt the methods of the exact sciences, recognizing that for permanent progress not only experiments are required but that the experiments should be of a quantitative character. It will be the purpose of this series of monographs to emphasize and further as much as possible this development of Biology.

Experimental Biology and General Physiology are one and the same science, by method as well as by contents, since both aim at explaining life from the physico-chemical constitution of living matter. The series of monographs on Experimental Biology will therefore include the field of traditional General Physiology.

Jacques Loeb,
T. H. Morgan,
W. J. V. Osterhout.

AUTHOR'S PREFACE

In preparing the material of a series of lectures, given at the Lowell Institute in Boston in December 1920, for book publication, I have deemed it on the whole best to adhere rather closely to the original lecture mode of presentation with all its informality. Except for the fact that the matter is here set forth in somewhat greater detail than was possible under the rigid time limitations of the Lowell Institute, and that the breaking into chapters is slightly different, the whole is substantially as it was presented in Boston.

What I tried to do in these lectures was to bring together under a unified viewpoint some of the more important contributions which have been made to our knowledge of natural death, from three widely scattered sources: namely general biology, experimental biology, and statistical and actuarial science. It will be obvious to anyone who knows the literature from these fields regarding natural death and the duration of life that in such an amount of space as is here used, no one could hope to cover a field so wide with anything approaching completeness. To do so would require a series of volumes in place of one small one. But this has in no wise been my object; I have instead hoped that the very incompleteness itself of this work, necessitated by my limitations of space and knowledge, might stimulate the reader to penetrate for himself further into the literature of this fascinating and important field of biology. To help him to start upon this excursion a brief bibliography is appended. It by no means completely covers the field, but may perhaps serve as an introduction.

I am indebted to a number of authors and publishers for permission to use illustrations and wish here to express my great appreciation of this courtesy. The individual sources for these borrowed figures are in every case indicated in the legends. To Dr. J. McKeen Cattell I am especially grateful for allowing me the use of the blocks from the magazine publication of this material in the Scientific Monthly; to Dr. Alexis Carrel for permission to use unpublished photographs of his tissue cultures; and, finally, to Professor T. H. Morgan for critically reading the manuscript and making many helpful suggestions.

R. P.

BALTIMORE,
April 19, 1922.

CONTENTS

ILLUSTRATIONS

see some sort of notion of immortality incorporated in an integral part of almost all folk philosophies of which any record exists.

Now, perhaps unfortunately, perhaps fortunately, it has up to the present time proved impossible absolutely to demonstrate, for reasons which will presently appear, by any scientifically valid method of experimentation or reasoning, that any real portion of that totality of being which is an individual living man persists after he dies. Equally, for the same reasons, science cannot absolutely demonstrate that such persistence does not occur. The latter fact has had two important consequences. In the first place, it has permitted many millions of people to derive a real comfort of soul in sorrow, and a fairly abiding tranquility of mind in general from the *belief* that immortality is a reality. Even the most cynical of scoffers can find little fault with such a result, the world and human nature being constituted as they are. The other consequence of science's present inability to lay bare, in final and irrefragable terms, the truth about the course, if any, of events subsequent to death is more serious. It opens the way for recurring mental epidemics of that intimate mixture of hyper-credulity, hyper-knavery, and mysticism, which used to be called spiritualism, but now usually prefers more seductive titles. We are at the moment in the midst of perhaps the most violent and destructive epidemic of this sort which has ever occurred. Its evil lies in the fact that in exact proportion to its virulence it destroys the confidence of the collective mind of humanity in the enduring efficacy of the only thing which the history of mankind has demonstrated to contribute to the real advancement of his intellectual, physical, spiritual and moral well being, namely that orderly progression of ascertained knowledge which we now call *science*.

The reason why science finds itself helpless to prevent spiritualism's insidious sapping of the intellectual fiber of the race is because it is asked to prove a negative, upon the basis of unreal data. How difficult such a task is is obvious as it is proverbial. Until science has demonstrated that there is *not* a continuation of individual supernatural existence after natural death, the spiritualist can, and will, come forward with supposed demonstrations that there is such a continuation. But the most characteristic feature of science is its actuality, its reality, its naturality. Pearson has pointed out, in characteristically clear and vigorous language, the reason why, in the minds of uninformed persons, science appears helpless in this situation. He says:

> Scientific ignorance may either arise from an insufficient classification of facts, or be due to the unreality of the facts with which science has been called upon to deal. Let us take, for example, fields of thought which were very prominent in medieval times, such as alchemy, astrology, witchcraft. In the fifteenth century nobody doubted the "facts" of astrology and witchcraft. Men were ignorant as to how the stars exerted their influence for good or ill; they did not know the exact mechanical process by which all the milk in a village was turned blue by a witch. But for them it was nevertheless a fact that the stars did influence human lives, and a fact that the witch had the power of turning the milk blue. Have we solved the problems of astrology and witchcraft today?
>
> Do we now know how the stars influence human lives, or how witches turn milk blue? Not in the least. We have learnt to look upon the facts themselves as unreal, as vain imaginings of the untrained human mind; we have learnt that they could not be described scientifically because they involved notions which were in themselves contradictory and absurd. With alchemy the case was somewhat different. Here a false classification of real facts was combined with inconsistent sequences—that is, sequences not deduced by a rational method. So soon as science entered the field of alchemy with a true classification and a true method, alchemy was converted into chemistry and became an important branch of human knowledge. Now it will, I think, be found that the fields of inquiry, where science has not yet penetrated and where the scientist still confesses

ignorance, are very like alchemy, astrology, and witchcraft of the Middle Ages. Either they involve facts which are in themselves unreal—conceptions which are self-contradictory and absurd, and therefore incapable of analysis by the scientific or any other method—or, on the other hand, our ignorance arises from an inadequate classification and a neglect of scientific method.

This is the actual state of the case with those mental and spiritual phenomena which are said to lie outside the proper scope of science, or which appear to be disregarded by scientific men. No better example can be taken than the range of phenomena which are entitled Spiritualism. Here science is asked to analyse a series of facts which are to a great extent unreal, which arise from the vain imaginings of untrained minds and from atavistic tendencies to superstition. So far as the facts are of this character, no account can be given of them, because, like the witch's supernatural capacity, their unreality will be found at bottom to make them self-contradictory. Combined, however, with the unreal series of facts are probably others, connected with hypnotic and other conditions, which are real and only incomprehensible because there is as yet scarcely any intelligent classification or true application of scientific method. The former class of facts will, like astrology, never be reduced to law, but will one day be recognized as absurd; the other, like alchemy, may grow step by step into an important branch of science. Whenever, therefore, we are tempted to desert the scientific method of seeking truth, whenever the silence of science suggests that some other gateway must be sought to knowledge, let us inquire first whether the elements of the problem, of whose solution we are ignorant, may not after all, like the facts of witchcraft, arise from a superstition, and be self-contradictory and incomprehensible because they are unreal.

Let us recapitulate briefly our discussion to this point. Mankind has endeavored to prolong the individual life by natural and by supernatural means. This latter plan falls outside the present purview of the scientific method. The former is, in last analysis, responsible for a considerable part, at least, of the development of the science of biology, pure and applied, and the arts which found their operations upon it. Biology can and has contributed much to our knowledge of natural death and the causes which determine the duration of life. It is the purpose of this book to review some of the more important aspects

of this phase of biological science, and endeavor to set forth in an orderly and consistent manner the present state of knowledge of the subject.

The problem of natural death has two aspects, one general, the other special. These may be stated in this way:

1. Why do living things die? What is the meaning of death in the general philosophy of biology?

2. Why do living things die *when* they do? What factors determine the duration of life in general and in particular, and what is the relative influence of each of these factors in producing the observed result?

Both of these problems have been the subject of much speculation and discussion. There has accumulated, especially in recent years, a considerable amount of new experimental and statistical data bearing upon them. I hope to be able in what follows to show that this new material, together with that which has for a long time been a part of the common store of biological knowledge, makes possible a clearer and more logically consistent picture than we have had of the meaning of death and the determination of longevity. Let us first examine in brief review the broad generalizations about death which have grown up in the course of the development of biology, and which may now be regarded as agreed to by practically all biologists.

BIOLOGICAL GENERALIZATIONS ABOUT NATURAL DEATH

The significant general facts which are known about natural death are these:

(A). *There is an enormous variation in the duration of life, both intra and inter-racially.* Table I, which is adapted from various authorities, is to be read with the

understanding that the figures are estimates, frequently based upon somewhat general and inexact evidence, and record extreme, though it is believed authentic instances. While the figures, on the accounts which have been mentioned, are subject to large probable errors, the table does give a sufficiently reliable general picture of the truth to indicate the enormous differences which exist among different forms of animal life in respect of longevity.

TABLE 1
Longevity of Animals

Animal	Approximate limits of maximum duration of life in different species
Lower invertebrates	Under 100 hours to ?
Insects	Under 100 hours to 17 years
Fish	? to 267 years
Amphibia	? to 36 years
Reptiles	? to 175 years
Birds	9 years to 118 years
Mammals	1½ years to over 100 years

We see from this table that life may endure in different forms from only the briefest period, measured in hours as in the case of *Ephemeridae,* to somewhere in the hundreds of years. The extremely long durations are of course to be looked upon with caution and reservation, but if we accept only extreme cases of known duration of life in man, the range of variation in this characteristic of living things is sufficiently wide.

It is probable that man, in exceptional instances, is nearly the longest lived of all mammals. The common idea that whales and elephants attain great longevity appears to be not well founded. The absolutely authentic instances of human survival beyond a century are, contrary to the prevalent view and customary statistics, extremely rare. The most painstaking and accurate

investigation of the frequency of occurrence of centenarians which has ever been made is that of T. E. Young. Because of the considerable intrinsic interest of the matter, and the popular misconceptions which generally prevail about it, it will be worth while to take a little time to examine Young's methods and results. He points out in the beginning that the evidence of great age which is usually accepted by census officials, by registrars of death, by newspaper reporters, and by the general public, is, generally speaking, of no validity or trustworthiness whatever. Statements of the person concerned, or of that person's relatives or friends, as to extreme longevity, can almost invariably be shown by even a little investigation to be extremely unreliable. To be acceptable as scientific evidence any statement of great age must be supported by unimpeachable *documentary* proof of at least the following points:

a. The date of *birth*, or of baptism.
b. The date of *death*.
c. The *identity* of the person dying at a supposed very advanced age with the person for whom the birth or baptismal record, upon which the claim of great age is based, was made out.
d. In the case particularly of married women the date of *marriage*, the person to whom married, and any other data which will help to establish proof of identity.

In presumptive cases of great longevity, which on other grounds are worthy of serious consideration, it is usually in respect of item c—the proof of identity—that the evidence is weakest. Every student of genealogical data knows how easy it is for the following sort of thing to happen. John Smith was born in the latter half of the eighteenth century. His baptism was duly and properly registered. He unfortunately died at the age of

say 15. By an oversight his death was not registered. In the same year that he died another male child was born to the same parents, and given the name of John Smith, in commemoration perhaps of his deceased brother. This second John Smith was never baptized. He attained the age of 85 years, and then because of the appearance of extreme senility which he presented, his stated age increased by leaps and bounds. A study of the baptismal records of the town disclosed the apparent fact that he was just 100 years old. The case goes out to the public as an unusually well authenticated case of centenarianism, when of course it is nothing of the sort.

Young applies vigorously the criteria above enumerated first, to the historically recorded cases of great longevity such as Thomas Parr, *et id genus omne*, and rejects them all; and second to the total mortality experience of all the Life Assurance and Annuity Societies of Great Britain and the annuity experience of the National Debt Office. The number of persons included in the experience was close upon a million. He found in this material, and from other outside evidence, exactly 30 persons who lived 100 or more years. In Table 2 the detailed results of his inquiry are shown in condensed form.

It will be noted from this table that the most extreme case of longevity which Young was able to authenticate was about a month and a half short of 111 years. Of the 30 centenarians recorded 21 were women and 9 were men. The superiority of women in expectation of life is strikingly apparent at the very high age of 100 years. We shall later see that this is merely a particularly noteworthy instance of a phenomenon which is common to a great portion of the life span.

The contrast between these proved findings of Young, exceedingly modest both in respect of numbers, and extremity of longevity, and the loose data on centenarianism

TABLE 2

Authentic Instances of Centenarianism (from Young)

Sex	Social status (single or married)	Age at death (or living)		
		Years	Months	Days
♀	M	110	..	321
♀	M	108	..	144
♀	M	105	8	...
♀	S	104	9	16
♀	M	103	9	28
♀	?	103	..	269
♀	M	103	3	7
♂	?	103	1	8
♂	?	102	9	2
♀	?	102	..	218
♀	S	102	2	10
♀	S	102	1	8
♀	S	102	..	21
♀*	S	102	..	19
♂	?	102	..	2
♀†	S	101	10	4
♀	S	101	8	25
♂	?	101	..	263
♂	?	101	4	...
♀	S	101	1	16
♀	S	101	1	4
♂	?	101	..	32
♀	S	101	..	1
♂	?	100	9	4
♀	S	100	7	6
♀	S	100	6	9
♀	M	100	..	133
♂	M	100	2	24
♀	S	100	1	10
♂	?	100	..	20

* Living 30 September, 1905.

† Living 31 July, 1898.

which one can find in any year's mortality statistics, is striking. In an examination of the matter recently, for example, it was found that in the registration area of the

United States there were recorded in the year 1916, out of a total of 1,001,921 deaths at all ages the following as of ages 100 or over:

White males	137
Colored males	116
White females	180
Colored females	216
Total	649

In this large total 4 persons were recorded as having died at the age of 120, and one, a colored female, at the preposterous age of 134!

B. *There is no generally valid, orderly relationship between the average duration of life of the individuals composing a species and any other broad fact now known in their life history, or their structure, or their physiology.* Many attempts have been made to set up generalizations establishing connections of this sort. Weismann particularly, has endeavored to establish such relations only to have them overthrown, sometimes by facts which he himself presents. It has, for example, been contended that the larger an animal the longer its life. This is obviously no general law. Again it has been held that no animal lives after reproducing, except such as care for their young, but almost numberless instances can be adduced where no such relationship holds. It will not pay to examine all the hypotheses of this general type which have, at one time or another, been put forward. With one exception, to which we shall advert immediately, they all suffer from too many important exceptions to be considered valid generalizations.

C. *Natural death as distinguished from accidental death is preceded by definite structural and functional*

FIG. 1. Photograph of John Shell, claimed to be 131 years old, but actually about 100, with his wife and putative son. (From Nascher).

changes in the body. These changes in the structure of different organs and parts of the body, and in their manner of functioning constitute the material basis of what is called *senescence* or growing old. Some of the morphological and physiological changes which characterize extreme senescence are apparent and known to all. Such are in case of man the bent posture which means an altered position and fusion of the elements of the vertebral column, the wrinkled visage, which denotes a profound alteration of tissue elements, and the shuffling and uncertain gait, which bespeaks a failing motor coördination. In Figure 1 these senescent changes are all well indicated in the case of an old man who has received much newspaper notice, "Uncle" John Shell of Kentucky, who is here shown with his last wife and supposed son. This poor old man has been exhibited about that part of the country as "the oldest living human being," at a claimed age of 131 years. As a matter of fact, Nascher, who has made a careful investigation of the case, finds him to be "about one hundred years old, possibly a year younger or older." The paternity of the 4½ year old boy, though claimed by Shell, is in considerable doubt.

Beside these obvious senescent changes there are going on even more significant changes in the cellular elements which compose the body. Certain of these cellular changes of age were described in a series of Lowell lectures given a little more than a decade ago by the late Dr. Charles Sedgwick Minot. Over a quarter of a century ago Hodge made a careful study of senile changes in nerve cells. In a man dying naturally at 92 years of age he found marked changes in the cells of the spinal ganglia as compared with those of a new born babe. The chief differences are exhibited in Table 3.

TABLE 3

Showing the Principal Differences Observed on Comparing the Spinal Ganglion Cells (First Cervical Ganglion) from a Child at Birth With Those from a Man Dying of Old Age at Ninety-two Years.

(From Hodge's data)

	Baby at birth. Male	Old Man
Volume of nucleus	100 per cent.	64.2 per cent.
Nucleoli visible	53 per cent.	5 per cent.
Deep pigmentation	0 per cent.	67 per cent.
Slight pigmentation	0 per cent.	33 per cent.

Hodge found still more marked changes in the antennary lobe of the nervous system of the honey bee. The nature of the changes is shown in Figure 2.

In the ganglion cells of both man and the honey bee, the volume of the nucleus in proportion to that of the rest of the cell body becomes reduced with advancing age. Minot showed that this was a very general phenomenon in senescence, and was a continuous process from birth to death. He gave to it and related and associated cellular changes the name "cytomorphosis," and attributed to it the greatest significance in bringing about senescence and death. As we shall presently see, cytomorphosis may perhaps more justly be regarded as one of the morphological results of senescence rather than its cause.

Recently Mrs. Pixell-Goodrich, an English worker, has re-studied the senescent changes in the cells of the honey bee. Her work shows in a striking way the loss of protoplasm in the aged cell. In the young bee immediately after hatching, the cells are large and plump, only separated from each other by narrow strands of connective tissue. In the same region of the same ganglion in an old bee which came from a hive on a fine day in March, but was too weak to effect a cleansing flight and soon became moribund, the nerve cells were quite worn out. There

was left only a framework of connecting tissue, with an occasional nucleus of a nerve cell in a more or less necrotic condition, with only a little cytoplasm around it.

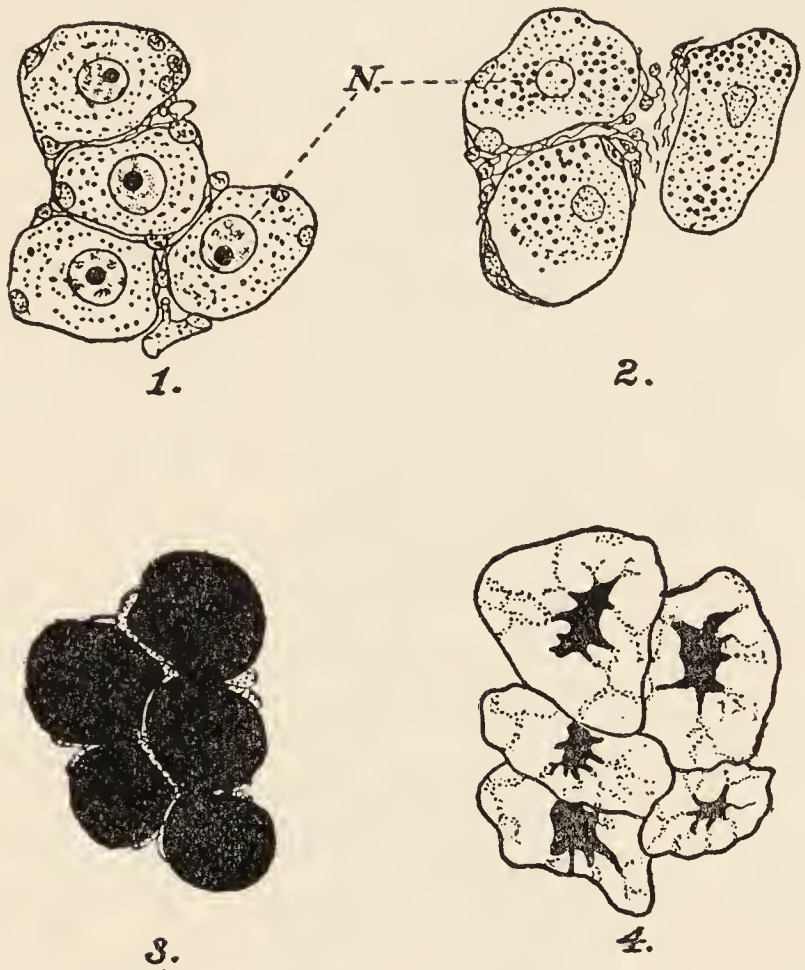


FIG. 2.—Showing the changes in nerve cells due to age. 1, spinal ganglion cells of a still-born male child; 2, spinal ganglion cells of a man dying at ninety-two years; N. nuclei. In the old man the cytoplasm is pigmented, the nucleus is small, and the nucleolus much shrunken or absent. Both sections taken from the first cervical ganglion, X 250 diameters; 3, nerve cells from the antennary ganglion of a honey-bee, just emerged in the perfect form; 4, cells from the same locality of an aged honey-bee. In 3, the large nucleus (black) is surrounded by a thin layer of cytoplasm. In 4, the nucleus is stellate, and the cell substance contains large vacuoles with shreds of cytoplasm. (From Donaldson after Hodge).

There are other and perhaps even more general and striking morphological changes in senescence than the changed relation between cytoplasm and nucleus. Conklin says:

By all odds the most important structural peculiarity of senescence is the increase of metaplasm or differentiation products at the expense of the general protoplasm. This change of general protoplasm into products of differentiation and of metabolism is an essential feature of embryonic differentiation and it continues in many types of cells until the entire cell is almost filled with such products. Since nuclei depend upon the

general protoplasm for their growth, they also become small in such cells. If this process of the transformation of protoplasm into differentiation products continues long enough it necessarily leads to the death of the cell, since the continued life of the cell depends upon the interaction between the general protoplasm and the nucleus. In cells laden with the products of differentiation, the power of regulation is first lost, then the power of division, and finally the power of assimilation; and this is normally followed by the senescence and death of the cells.

D. *Natural death (as distinguished from accidents) occurs normally and necessarily only in animals composed of many cells.* Unicellular organisms are finally known, to a considerable extent as the result of the brilliant and painstaking researches of Woodruff and his students, to be immortal *in esse* as well as *in posse.* Since the discovery by Woodruff and Erdman of the process of nuclear reorganization, which they call endomixis, this conclusion is as solidly grounded if we regard a cycle of protozoan divisions as the homologue of the metazoan body, as it is if we consider each individual protozoan as such homologue. Woodruff has been cultivating the common unicellular form *Paramecium,* shown in Figure 3, for over 13 years.

During all this time no conjugation or pairing of individuals has occurred. In a recent letter Dr. Woodruff says: "After we had discovered and worked out endomixis there seemed no particular use of carefully recording the number of generations each day. But the culture is still going on as well as ever and is at approximately the 8500th generation—13½ years old! On May 1, 1915, (just 8 years old) it was at the 5071st generation." If in 8500 generations—a duration of healthy reproductive existence which, if the generation were of the same length as in man would represent roughly a quarter of a million years in absolute time—natural death has not

occurred, we may with reasonable assurance conclude that this animal is immortal.

Of even more probative value, in the opinion of some workers, than the results on *Paramecium* are

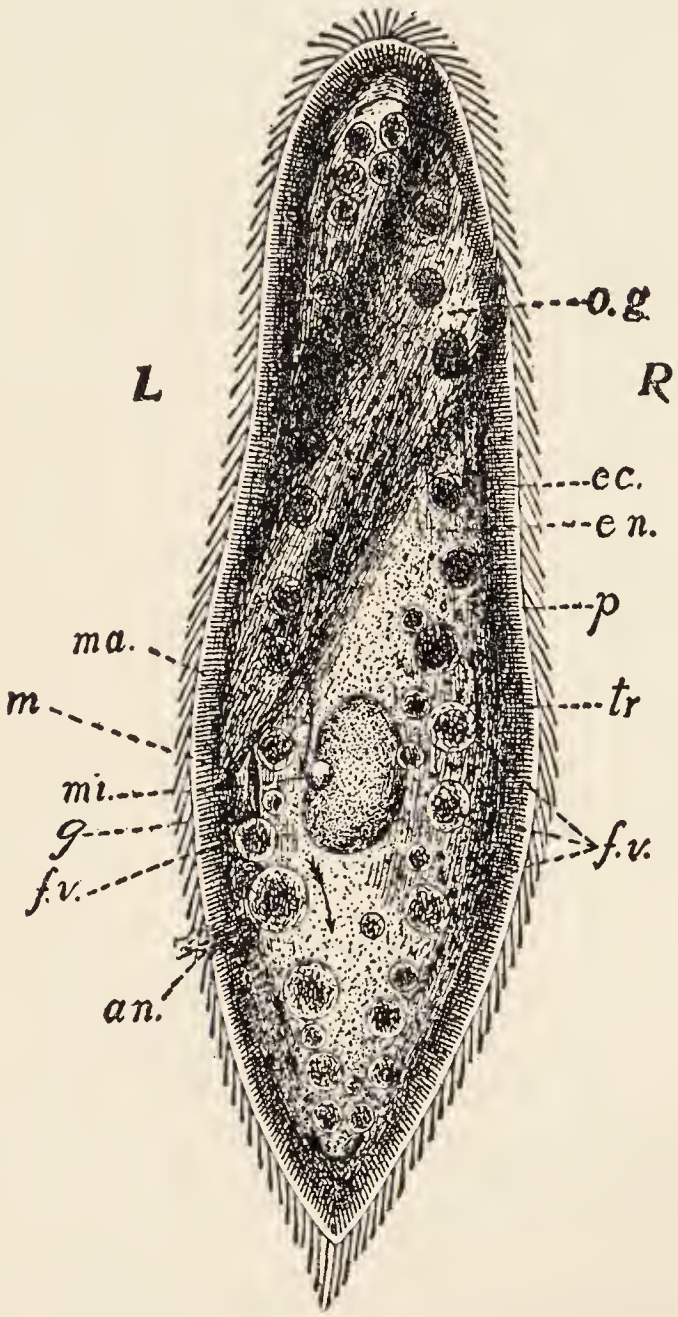


FIG. 3.—Paramecium, viewed fron the oral surface. *L.* left side; *R*, right side; *an.*, anus; *ec.*, ectosarc; *en.*, endosarc; *f. v.*, food vacuoles; *g*, gullet; *m*, mouth; *ma.*, macronucleus; *mi.*, micronucleus; *o. g.*, oral groove; *P.*, pellicle; *tr.*, trichocyst layer. The arrows show the direction of movement of the food vacuoles. (From Jennings).

the recent experiments of Hartmann, who cultivated *Eudorina elegans* for over 600 generations without conjugation or any nuclear reorganization corresponding to endomixis, and no depression in the culture occurred.

The distinction between Protozoa and Metazoa in

respect of the incidence of natural death is so important that it requires a somewhat detailed explanation, together with the reasons for it. Protozoa reproduce by a process of simple division or fission. A particular individual after growing to a certain size simply divides transversely into two like individuals, at first smaller in size, but ra-

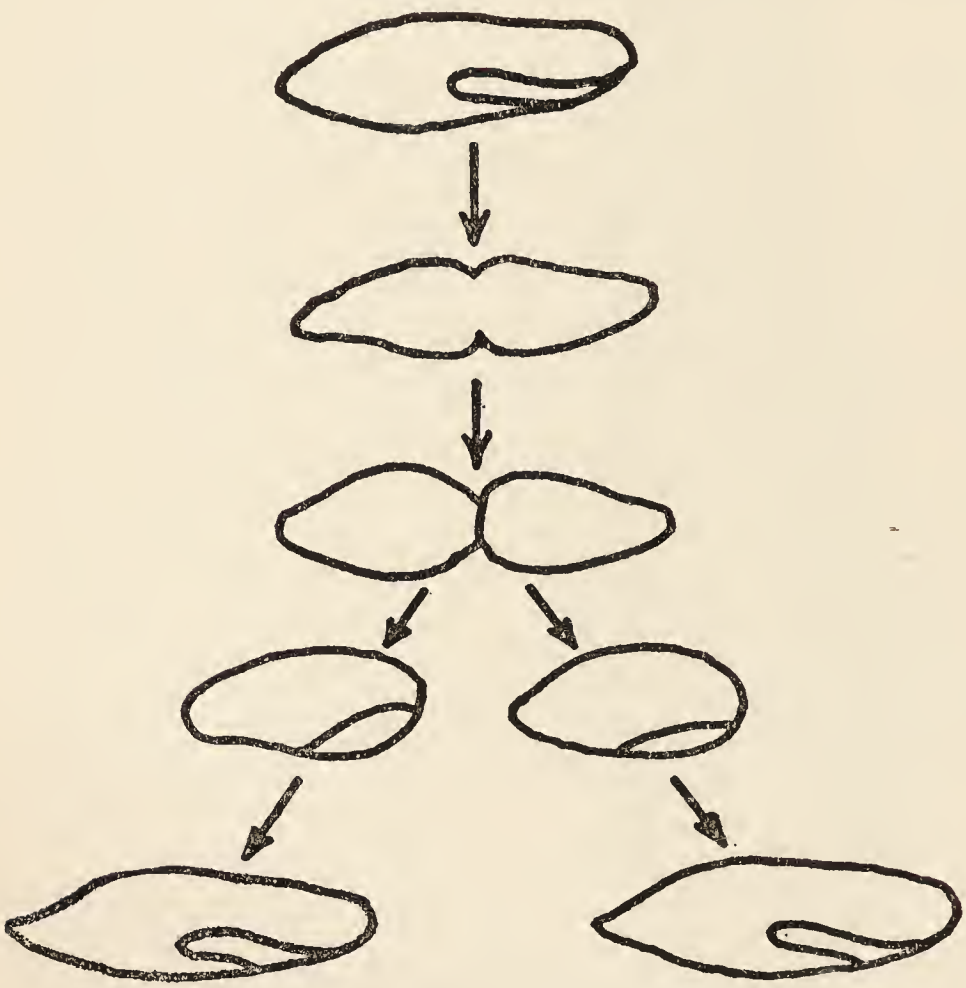


Fig. 4—Diagram showing the process of reproduction by fission in the unicellular orginism *Paramecium*.

Fig. 5—Conjugation in Paramecium.

pidly growing to full adult magnitude. The essential gross features of this process are illustrated in Figure 4. One cannot say, after the act of fission is accomplished, which is parent and which is offspring. One individual simply becomes two and, in the process of becoming two, loses totally its own identity as an individual. Upon occasion another process known as *conjugation* may intervene.

In this process two individuals mate together. By a process of assortative mating, like sizes pair together,

as was first shown by the writer and later confirmed by Jennings. After pairing has occurred an interchange of nuclear substance occurs by a mechanism described and figured in many elementary textbooks of zoology. This process of conjugation need not further concern us here, for the reason that Woodruff, in the work already referred to, has shown that this phenomenon is not essential to the continued life of the race. Its place may be, and normally very frequently is, taken by the process called endomixis. In this process there occurs a nuclear breakdown and reorganization which appears to be the equivalent, functionally at least, of that which takes place during conjugation.

There has been much discussion, particularly among European workers, as for example Doflein, Jollos, Wedekind, Slotopowski, and others, about certain philosophical, not to say metaphysical, aspects of immortality in the Protozoa. But all such discussion has in no wise disturbed or altered the plain physical fact that there is no place for death in a scheme of reproduction by simple fission, such as is illustrated in Figure 4. Nothing is left at any stage to fulfill the proverbial scheme of "dust to dust and ashes to ashes." When an individual is through its single individual existence it simply becomes two individuals, which go on playing the fascinating game of living here and now.

In a few of the simplest and most lowly organized groups of many-celled animals or Metazoa this power of multiplication by simple fission, or budding off a portion of the body which reproduces the whole, is retained as a facultative asset. This process of reproduction in which the somatic or body cells of one generation produce the somatic cells of the next generation has been called agamic reproduction. It occurs as the more usual but not

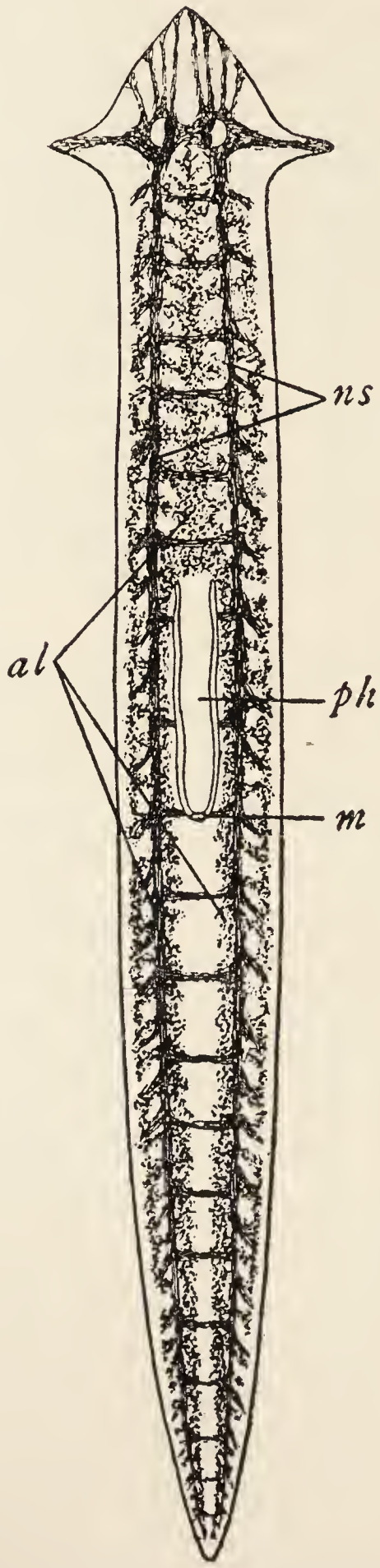


FIG. 6.—Planaria dorotocephala: *m*, mouth; *ph*, pharnyx: *al*, alimentary tract; *ns*, nervous system. (From Child).

exclusive mode of reproduction, in some or all forms of the three lowest groups of multicellular organisms, the sponges, flatworms, and coelenterates. More rarely it may occur in other of the lower invertebrate groups. It may occur in the form of budding or of fission comparable to that of the *Protozoa.* The agamic reproduction of one of the flatworms, *Planaria dorotocephala,* studied by the writer many years ago, as shown in Figure 6, may serve as an illustration.

Fig.—7. Beginning of process of agamic reproduction by fission in planaria. (From Child)

This simply organized worm, which lives under stones in sluggish streams and ponds, after attaining a certain size, will under the appropriate environmental conditions exhibit a constriction towards the posterior end of the body, as shown in Figure 7.

For a time the animal moves about as a rather ungainly double individual. It finally separates into two. The larger anterior part forms a new tail, and the smaller posterior fission product forms a new head and rapidly grows to full size. The process is, in principle, exactly the same as the multiplication of Paramecium by fission. In another member of the same general group of animals as *Planaria,* named *Stenostomum,* several fission planes may form and the process start anew before the products delimited by the first plane have separated. As a result, we get frequently in this form chains of individuals attached in a long string to each other, as shown in Figure 8.

It is obvious that so long as reproduction goes on in

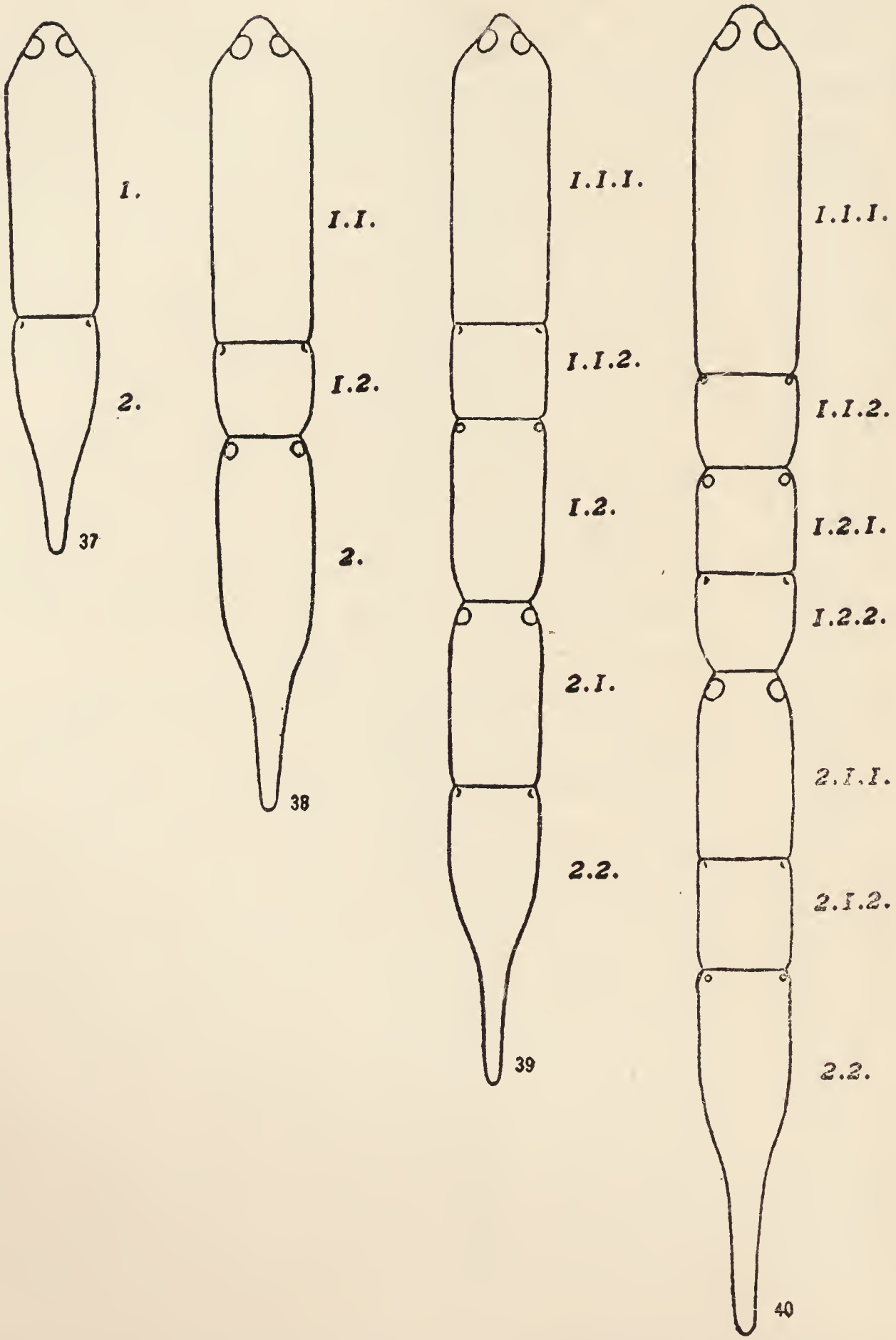


Fig. 8—Progress of agamic reproduction in Stenostomum: the sequence in the formation of new zooids is indicated by the numerals. (From Child.).

this manner in these multicellular forms there is no place for death. In the passage from one generation to the next no residue is left behind. Agamic reproduction and its associated absence of death occurs very commonly in plants. Budding and propagation by cuttings are the common forms in which it is seen. The somatic cells have the capacity of continuing multiplication and life for an indefinite duration of time, so long as they are not accidentally caught in the breakdown and death of the whole individual in which they are at the moment located. Thus virtually every apple tree in every orchard in this country is simply a developed branch or bud of some original apple tree from which it was cut, in many cases centuries ago. Apple trees cannot of their own unaided efforts propagate either buds or cuttings. So, until the intervention of man, some apple trees died natural deaths, somatically speaking, just as do the higher animals of which we shall speak presently. But their cells were inherently capable of better things, as was demonstrated when man first cut off a shoot from an old apple tree and provided it with a root by grafting.* Then it went on and made a new tree. From it in turn cuttings were taken, and so the process has continued to the present day. A part of the soma of one generation produces the soma of the next generation and goes on living indefinitely.

A different mode of reproduction is characteristic of higher multicellular animals, and in all but the lowest groups is the exclusive method. A new individual is started by the union of two peculiar cells of extraordinary potentialities, called germ cells. These germ cells are of two sorts, ova and spermatozoa. In bisexual organisms

* This provision of roots was not essential, only practically convenient. The cutting would, if enough pains were taken, grow its own roots.

the former are borne in the female, and the latter in the male body. Both sorts undergo a complicated preparation for union, the result of which is that when union does occur each party to it contributes either an exactly equal or an approximately equal amount of hereditary mate-

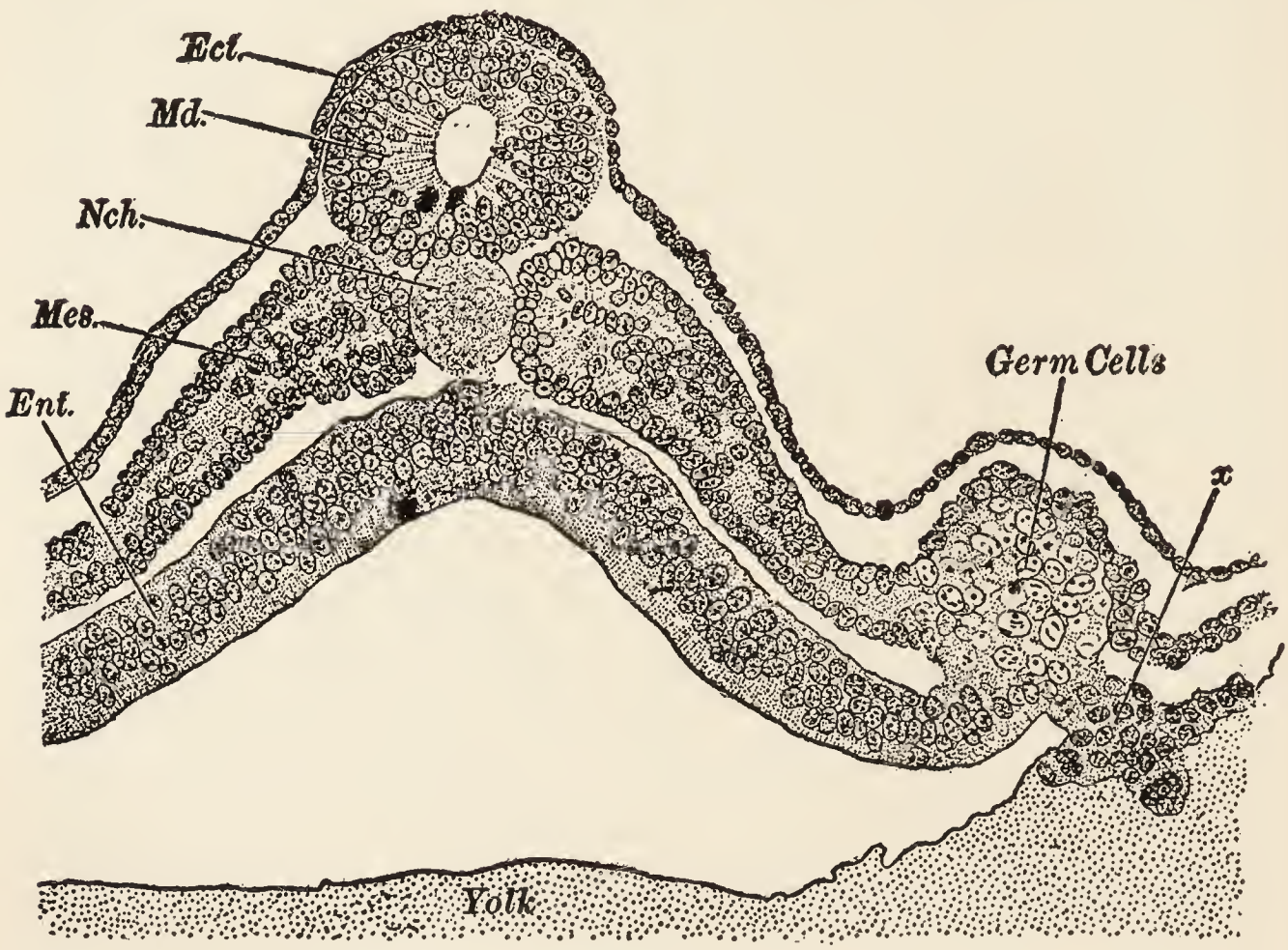


Fig. 9.—Section across the posterior part of an embryo dog-fish (acanthias) of 3.5 mm., to show the compact cluster of germ cells on one side. The germ cells in later stages migrate from this primative position, moving singly or in small groups. *Ect*, ectoderm: *Md*, medullary canal or primitive spinal cord; *Nch*, notochord; *Mes*, mesoderm: *Ent*, entoderm: *X*, cellular strand connecting the germ cell cluster with the yolk. (From Minot after Woods, with the permission of the publishers, G. P. Putnam's Sons).

rial. After union has taken place the fertilized ovum or zygote presently begins to divide, first into two cells, these again to four and so on, until by a continuation of this process of division with concomitant differentiation the whole body is formed. As the animal develops by repeated cell division and differentiation, it is frequently found that at the very early stage the cells which are to be the germ cells of the next generation are clearly re-

cognizable by their structure, and often are set aside in a definite location in the developing embryo. Thus, to take but a single example of a phenomenon of wide generality, at a very early stage in the development of the dog-fish, when the only bodily organs of which even the rudiments are recognizable are the beginnings of what will presently become the spinal cord and the back-bone,

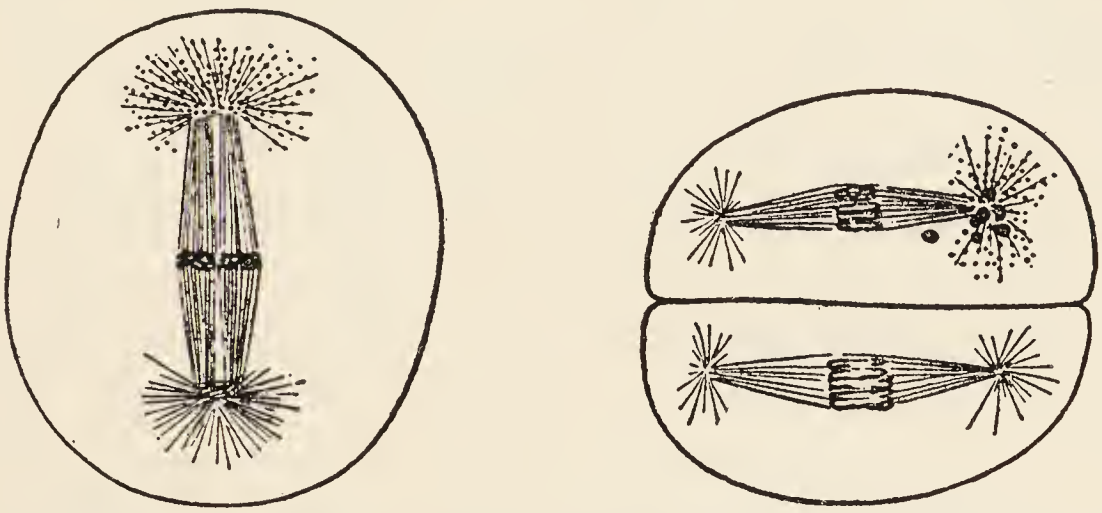


Fig. 10.—First division in egg of Cyclops, showing at one pole of spindle the granules which mark the germ path. (From Child, after Amma, by permission of University of Chicago Press).

it was shown by Woods, many years ago, that the germ cells are definitely localized and recognizable, as shown in Figure 9.

In some forms, notably the round-worm *Ascaris*, various crustacea and insects, the cells which are to become germ cells are visibly set apart from the very first or one of the first three or four cleavages of the fertilized ovum. For example, in the case of the crustacean *Cyclops*, Amma has shown that the granules visible at one pole in the very first division mark the prospective germ path, as shown in Figure 10.

In the gnat *Chironomus* the same thing is visible at a very early cleavage, according to the observations of Harper. For a comprehensive and critical review of the

extensive literature on the *Keimbahn* one should consult the recent contributions of Hegner on the subject.

To condense a long and complicated matter we may state the situation regarding reproduction and death in the *Metazoa* in this way. A higher, multicellular individual may be conceived, from the viewpoint of the present discussion, as composed of two essentially independent portions: the germ cells on the one hand, which are immortal in the same sense that the Protozoa are immortal, and the rest of the body, which it is convenient to call technically the soma, on the other hand. The soma undergoes natural death after an interval of time which, as we have seen, varies from species to species. The germ cells which the individual bears in its body at the time of its death of course die also. But this is purely accidental death so far as concerns the germ cells. Such of them as were, prior to the death of the soma, enabled to unite with other germ cells went on living just as does the dividing *Paramecium*. Reduced to a formula we may say that the fertilized ovum (united germ cells) produces a soma, and more germ cells. The soma eventually dies. Some of the germ cells, prior to that event, produce somata and germ cells, and so on in a continuous cycle which has never yet ended since the appearance of multicellular organisms on the earth.

The contrast between the protozoan and the metazoan method of descent is shown in Figure 11, which is a modification of a similar diagram originally due to my colleague, Dr. H. S. Jennings.

The diagram represents the descent of generations. The upper portion of the diagram shows the mode of descent in forms reproducing from organisms reproducing from a single parent. The lower, or B portion of the

diagram shows the mode of descent in form reproducing from two parents. The lines represent the lives of individuals (as in A diagram), or of germ cells (in the B

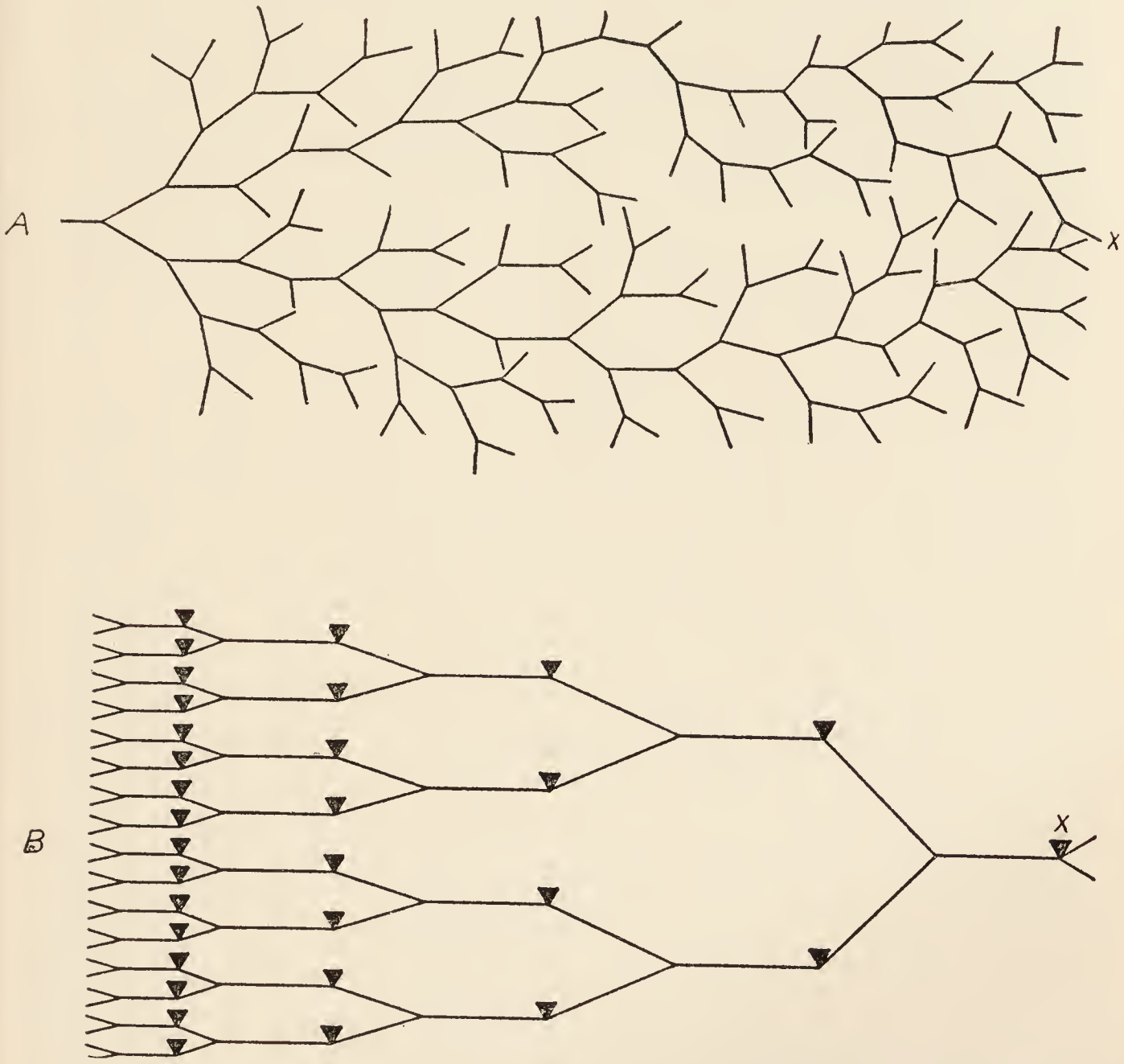


FIG. 11. Diagram to show mode of descent in (A) unicellular animals reproducing agamically, and in (B) multicellular animals reproducing by germ cells. For further explanation see text. (Modified from Jennings).

diagram) beginning at the left and passing to the right. In the A diagram, which represents uniparental reproduction by fission, the line of ancestry traced back from any individual at the right is always single, and there is no corpse to be found anywhere, each present body transforming directly into the two bodies of the next generation.

In the B diagram, where we have bi-parental reproduction by the union of germ cells, as in man, the solid black triangles represent the bodies, or somata, and the lines the germ cells. A line of ancestry traced back from any individual towards the right end of the diagram forks at each generation, and in comparatively few generations one has a multitude of ancestors. The *bodies* of one generation have no continuity with the bodies of the previous or the following generation. In each generation the soma dies, while new somata are reproduced by the union of germ cells from diverse lines.

E. *Life itself is a continuum.* A break or discontinuity in its progression has never occurred since its first appearance. Discontinuity of existence appertains not to life, but only to one part of the makeup of a portion of one large class of living things. This is certain, from the facts already presented. Natural death is a new thing which has appeared in the course of evolution, and its appearance is concomitant with, and evidently in a broad sense, caused by that relatively early evolutionary specialization which set apart and differentiated certain cells of the organism for the exclusive business of carrying on all functions of the body other than reproduction. We are able to free ourselves, once and for all, of the notion that death is a necessary attribute or inevitable consequence of life. It is nothing of the sort. Life can and does all the time go on without death. The somatic death of higher multicellular organisms is simply the price they pay for the privilege of enjoying those higher specializations of structure and function which have been added on as a side line to the main business of living things, which is to pass on in unbroken continuity the never-dimmed fire of life itself.

THEORIES OF DEATH

On the basis of these five general classes of facts which have been briefly reviewed a whole series of speculations as to the meaning of death have been reared. The first attempt at a biological evaluation* of the meaning of death which attracted the serious attention of scientific men was that of Weismann. In his famous address of 1881 on the duration of life, Weismann propounded the thesis that death was an adaptation, advantageous to the race, and had arisen and was preserved by natural selection. Probably no more perverse extension of the theory of natural selection than this was ever made. It appeared, however, just at the time when the post-Darwinian attempt to settle the problems of evolution by sheer dialectic was at the zenith of its popularity. Nowadays such a doctrine as Weismann's would not receive so respectful a hearing.

Metchnikoff, whose views excited so much popular interest some years ago, held that death was the result of intoxication, arising from the absorption of putrefactive products of the activity of intestinal bacteria. The chief difficulty with this view is that it is demonstrably not true; either particularly in the case of man, where it can easily be shown that many statistically important causes of death cannot possibly be accounted for under it, or generally in the animal kingdom; because a number of cases are now known where a metazoan form can be successfully made to lead a completely aseptic life, and still death occurs at about the usual time. (Cf. Chapter VIII). More speculative developments of the same

* An excellent discussion of various theories of death, which the writer, though differing from some of the conclusions, has found useful in the preparation of this section, has lately been given by Child in his "Senescence and Rejuvenescence."

basic idea have been presented by Jickeli and Montgomery. Both held that because of the mechanical incompleteness of the processes of metabolism, injurious and toxic substances tend to accumulate in the cells of the body, and that senescence and death are the results of such accumulations.

A much broader, and in the light of all facts sounder view, is that the determination of degrees of longevity and of the fact of death itself, is inherent in the innate, hereditarily determined biological constitution of the individual and the species. This view was expressed by Johannes Müller a quarter of a century ago in his *Physiologie,* by Cohnheim forty years later, and has had many later adherents. I shall return to a discussion of it later.

There have been a number of theories of senescence and death, differing widely in details, but having the one point in common of attributing these phenomena to orderly changes with advancing age in the relative proportion of nucleus to protoplasm in the cells of the body. Here may be mentioned, without pausing to go into detailed consideration of their different views, Verworn, Mühlmann, Richard Hertwig, and Minot.

Another group of hypotheses, all advanced in comparatively recent times and associated with the names of Kassowitz, Conklin, and Child, are developed about the metabolic aspects of age changes. There is observed a decrease in assimilatory capacities of cells with differentiation and age. These metabolic changes are regarded as fundamentally casual of the phenomena of senescence and death. In this general group of hypotheses would belong the views of my colleague, Dr. W. T. Howard.

Benedict in a detailed investigation of senility in plants reaches the conclusion:

"that the duration of life is directly linked with the degree of permeability in that part of the living cell which places it in contact with the universe about it, and that as the activities of life proceed the cell is being gradually entombed by an inevitable decrease in the permeability of its protoplasm.

While decreasing permeability furnishes a possible explanation of the more obvious symptoms of senility, it cannot be the only degeneration of first rank. All protoplasmic functions must be involved. Underlying these primary causes of senile degeneration there must be some general fundamental cause from which they spring. This fundamental cause may well be the colloidal nature of protoplasm."

Delage and Jennings have considered that death is the result of differentiation. Jennings has put the matter in this way.....

"the continuity of life in the infusoria is in principle much like that in ourselves, though with differences in details. As individuals, the infusoria do not die, save by accident. Those that we now see under our microscopes have been living ever since the beginnings of life; they come from division of previously existing individuals. But in just the same sense, it is true for ourselves that everyone that is alive now has been alive since the beginning of life. This truth applies at least to our bodies that are alive now; every cell of our bodies is a piece of one or more cells that existed earlier, and thus our entire body can be traced in an unbroken chain as far back into time as life goes. The difference is that in man and other higher organisms there have been left all along the way great masses of cells that did not continue to live. These masses that wore out and died are what we call the bodies of the persons of earlier generations; but our own bodies are not descended by cell division from these; they are the continuation of cells that have kept on living and multiplying from the earliest times, just as have the existing infusoria."

Jennings' views regarding senescence in the protozoa will be discussed in the next chapter.

Unicellular organisms, as we have seen, do not normally experience natural death. In the higher organisms there has been a progressive setting apart of cells and tissues to perform *particular* vital functions with a consequent loss of the ability to perform *all* vital functions independently. As soon as any one of these cells or tissues begins, for any accidental cause whatever, to fail to per-

form its special function properly, it upsets the delicate balance of the whole associated community of cells and tissues. Because of the differentiation and specialization of function, the parts are mutually dependent upon each other to keep themselves and the whole going. Consequently any disturbance in the balance which is not promptly righted by some regulatory process must eventually end in death.

Since the publication of this material in serial form an objection to the foregoing statement has been suggested on the ground that differentiation *per se* does not appear to the critic to have much to do with the question of natural death in the Metazoa. To quote; "rather it is the failure *after differentiation* to keep up indefinitely the state reached. If, from any internal or external accident, the differentiated part suffers injury, the injury cannot be made good any more, since in *certain organs* this power has been lost. Hence, in time, loss after loss occurs and the machine wears out. The protozoan is as highly differentiated as any cell of a metazoan (or much more so); but since it "multiplies by dividing," it has retained the power to make good any loss. Therefore, it is not the differentiation *per se,* but the loss of power to repair that produces senescence."

This seems to me to be in the main only a somewhat different form of statement of precisely the idea that I have endeavored to express. When I have used the term "differentiation" in this connection, I have always had in mind, as one of its most important physiological concomitants, just the thing spoken of above. Furthermore, whether the protozoan *cell* is as highly differentiated as a metazoan cell, is not to the point at all. For, to have any pertinence so far as the present issue is concerned, the comparison must be between the differentiated proto-

zoan cell, *and the whole metazoan soma,* not one of its constituent cells. In the protozoan, all the differentiations are in and a part of one single cell operating as one metabolic unit, of small absolute size, and consequently easier and more labile internal physico-chemical regulation. In the metazoan soma we have organ differentiation, with the constituent cells in each organ highly specialized functionally, and dependent upon the normal functional activity of wholly other organs in order that they may keep going at all. Remove these tissue cells from the soma, and provide them with an abundance of suitable nourishment and oxygen, as in tissue cultures, and, so far as the evidence now available indicates, they will live forever (cf. Chapter II).

Consider for a moment the most highly differentiated protozoan known, on the one hand, and man, on the other hand, purely as physico-chemical machines, which only keep going if the internal balances and adjustments are, in each case, held within a narrow zone of normality. Quite aside from any question of their different modes of reproduction, the two machines are not equivalent, *as machines,* because of:(a) unicellular versus multicellular structure, (b) great absolute difference in size of the whole machines, with consequent requirement of an enormously more complex internal regulatory mechanism in the one case than in the other, whatever the inherent nature of this mechanism may be.

Essentially the same view of the matter as that held by the present writer has been well set forth by Loeb in his most recent paper on the subject. He says:

"All this points to the idea that death is not inherent in the individual cell, but is only the fate of more complicated organisms in which different types of cells or tissues are dependent upon each other. In this case it seems to happen that one or certain types of cells produce a substance or substances which gradually become harmful to a vital organ like the res-

piratory center of the medulla, or that certain tissues consume or destroy substances which are needed for the life of some vital organ. The mischief of death of complex organisms may then be traced to the activity of a black sheep in the society of tissues and organs which constitute a complicated multicellular organism."

At this point I shall not stay to discuss critically each of the hypotheses so summarily reviewed. Instead, I shall make bold to state somewhat categorically my own views on the origin and meaning of death and the determination of longevity; and in what follows, shall endeavor to set forth in orderly array the evidence which seems to me to support these views. In this process, the relations of what I shall suggest to the conclusions of earlier investigators will, I think, sufficiently appear.

Let us consider, then, the following picture of life and death:

1. Life itself is inherently continuous.

2. Living things, whether single-celled or many-celled organisms, are essentially only physico-chemical machines of extraordinary complexity; but regardless of their degree of complexity only amenable to, and activated in accordance with, physical and chemical laws and principles.

3. The discontinuity of death is not a necessary or inherent adjunct or consequence of life, but is a relatively new phenomenon, which appeared only when and because differentiation of structure and function appeared in the course of evolution.

4. Death necessarily occurs only in such somata of multicellular organisms as have lost, through differentiation and specialization of function, the power of reproducing each part if it, for any accidental reason breaks down or is injured; or still possessing such power in their cells, have lost the necessary mechanism for separating a

part of the soma from the rest for purposes of agamic reproduction.

5. Somatic death results from an organic disharmony of the whole organism, initiated by the failure of some organ or part to continue in its normal harmonious functioning in the entire differentiated and mutually dependent system. This functional breakdown of a part may be caused in a multitude of ways from external or internal sources. It may manifest itself in a great variety of ways both structurally and functionally. Many of these manifestations which have been regarded as causes of senescence, may more truly be considered concomitant attributes of senescence.

6. As a consequence of our second thesis which postulated life to be a mechanism, death, whether of a single somatic cell or of a whole soma, is a result of physico-chemical changes in the cell or organism; and these changes are in accordance with ordinary physico-chemical laws and principles.

7. The time at which natural death of the soma occurs is determined by the combined action of heredity and environment. For each organism there is a specific longevity determined by its inherited physico-chemical constitution. This specific longevity is capable of modification, within relatively narrow limits, as a result of the impact of environmental forces; the chief mode of action of the environment being in the direction of determining the rate at which the inherited endowment is used up.

For no one of the separate elements of this picture can I claim any particular originality. Most of them would probably be agreed to at once, at least by some biologists. The need is for a synthesizing into a consistent whole of a wide range of data, which have accumulated in various

fields of biology, about death and the duration of life. Such a synthesis will be attempted in what follows. Generally, those who have speculated about the biology of death have drawn their evidence from, or at least had their thinking largely colored by the facts in a relatively small part of the whole field. In particular, few biologists have any detailed knowledge of the most impressive mass of material, both in respect of quality and quantity, which exists regarding the duration of life of any organism. I refer, of course, to the enormous volume of rather exact data regarding human mortality. Much of this material, to be sure, wants proper analysis, not only mathematical but biological. But, that it is a rich material admits of no doubt.

CHAPTER II

CONDITIONS OF CELLULAR IMMORTALITY

In the preceding chapter it was pointed out that the germ cells of higher organisms are potentially, and under certain conditions in fact, immortal. What are the conditions of immortality in this case? Are they such as to support the thesis that the processes of mortality are essentially physico-chemical in nature, and follow physico-chemical laws?

ARTIFICIAL PARTHENOGENESIS

The most essential condition of this immortality of germ cells was mentioned, but not particularly emphasized. It is that two germ cells, an ovum and a spermatozoon *unite*, the process of union being called fertilization. Having united, if they then find themselves in appropriate environmental conditions, development goes on; new germ cells and a soma are formed, and the same process keeps up generation after generation. Now, while union of the germ cells is generally and in most organisms an essential condition of this process, it is also true that in a few forms of animal life, mostly found among the invertebrates, development of the ovum can take place without any preceding fertilization by a spermatozoon. The process of reproduction, in this case is called *parthenogenesis*. In a number of forms in which parthenogenesis never occurs normally, so far as is known, it can be induced by appropriate extraneous procedures. The discovery of this extraordinarily interesting and important fact for a number of organisms, and the careful

working out of its physico-chemical basis, we owe to Dr. Jacques Loeb, of the Rockefeller Institute for Medical Research. Artificial parthenogenesis may be induced, as Guyer, Bataillon and Loeb have shown, even in so highly organized a creature as the frog, and the animal may grow to full size. The frogs shown in Figure 12, while they present an appearance much the same as that of any other frog of the same species, differ in the rather fundamentally important respect that they had no father.

The rôle of a father was played in these cases by an ordinary dissecting needle. Unfertilized eggs from a virgin female were gently pricked with a sharply pointed needle. This initiation of the process of development took place March 16, 1916, in one case, and February 27, 1917, in the other. The date of death was, in the first case, May 22, 1917, and in the other March 24, 1918.

In the course of Loeb's studies of parthenogenesis in lower marine invertebrates, he became interested in the question of the death of the germ cells which had failed to unite, or, having united, failed of appropriate environmental conditions. His researches throw light on some of the conditions of cellular death, and on that account they may be reviewed briefly here. He found that the unfertilized mature eggs of the sea-urchin die comparatively soon when deposited in sea-water. The same eggs, however, live much longer, and will, if appropriate surrounding conditions are provided, go on and develop an adult organism, if they are caused to develop artificially by chemical means or naturally by fertilization. Loeb concluded from this that there are two processes going on in the egg. He maintained, on the one hand, that there are specific processes leading to death and disintegration; and, on the other hand, processes which lead to cell divi-

FIG. 12.—Artificially parthenogenetic frogs. (Loeb.)

sion and further development. The latter processes may be regarded as inhibiting or modifying the mortal process. Loeb and Lewis[1] undertook experiments, based upon this view, to see whether it would be possible by chemical treatment of the egg to prolong its life. Since in general specific life phenomena are perhaps, on the chemical side, chiefly catalytic phenomena, it was held to be reasonable that if some substance could be brought to act on the egg, which would inhibit such phenomena without permanently altering the constitution of the living material, the life of the cell should be considerably prolonged. The first agent chosen for trial was potassium cyanide, KCN. It was known that this substance weakened or inhibited entirely a number of enzymatic processes in living material, without materially or permanently altering its structure.

It was found that, normally, the unfertilized egg of the sea-urchin would live in sea-water at room temperature, and maintain itself in condition for successful fertilization and development, up to a period of about twenty-three hours. After that time the eggs began to weaken. Either they could not be successfully fertilized, or if they were fertilized, development only went on for a short time. After 32 hours, the eggs could not, as a rule, be fertilized at all. The experiment was then tried of adding to the sea-water, in which the unfertilized eggs were kept, small amounts of KCN in a graded series, and then examining the results of fertilizations undertaken after a stay of the unfertilized eggs of 75 hours in the solution. It will be noted that this period of 75 hours is more than three times the normal duration of life of the cell in normal sea-water. The results of this experiment are shown in summary form in Table 4.

TABLE 4

Experiments of Loeb and Lewis on the Prolongation of Life of the Sea-urchin Egg by KCN

Concentration of KCN	Result of fertilization after a 75 hours' stay in the solution
Pure sea-water	No egg segments
n/64000 KCN	No egg segments
n/16000 KCN	No egg segments
n/8000 KCN	Very few eggs show a beginning of segmentation
n/4000 KCN	Very few eggs show a beginning of segmentation
n/2000 KCN	Few eggs go through the early stages of segmentation
n/1000 KCN	Many eggs segment and develop into swimming larvæ
n/750 KCN	Many eggs segment and develop into swimming larvæ
n/400 KCN	A few eggs develop into swimming larvæ
n/300 KCN	No egg segments
n/250 KCN	No egg segments
n/200 KCN	No egg segments
n/100 KCN	No egg segments

From this table it is seen that in concentrations of KCN from n/750 to n/1000 the eggs developed perfectly into swimming larvæ. In other words, by the addition of this very small amount of KCN, the life period has been prolonged to three times what it would normally be under the same environmental conditions. Concentrations of KCN weaker than n/1000 were incapable of producing this result, or at best, if development started, the process came very quickly to an end. In stronger concentrations than n/400 the eggs were evidently poisoned, and no development occurred.

Other experiments of Loeb's show that the lethal effects of various toxic agents upon the egg cell may be inhibited or postponed for a relatively long time, by

suitable chemical treatment, such as lack of oxygen, KCN, or chloral hydrate. A typical experiment of this kind made upon the sea-urchin, *Strongylocentrotus purpuratus* may be quoted:

Eggs were fertilized with sperm and put eleven minutes later into three flasks, each of which contained 100 c. c. of sea-water + 16 c. c. 2-½ m $CaCl_2$. One flask was in contact with air, while the other two flasks were connected with a hydrogen generator. The air was driven out from these two flasks before the beginning of the experiment. The eggs were transferred from one of these flasks after four hours and fourteen minutes, from the second flask after five hours and twenty-nine minutes, into normal (aerated) sea-water. The eggs that had been in the hypertonic sea-water exposed to air were transferred simultaneously with the others into separate dishes with aerated normal sea-water. The result was most striking. Those eggs that had been in the hypertonic sea-water with air were all completely disintegrated by "black cytolysis." Ten per cent. of the eggs had been transformed into "shadows" (white cytolysis). It goes without saying that all the eggs that had been in the aerated hypertonic sea-water five and a half hours were also dead. The eggs that had been in the same solution in the absence of oxygen appeared all normal when they were taken out of the solution, and three hours later—the temperature was only 15°C.—they were all, without exception in a perfectly normal two- or four-cell stage. The further development was also in most cases normal. They swam as larvæ at the surface of the vessel and went on the third day (at the right time) into a perfectly normal pluteus stage, after which their observation was discontinued. Of the eggs that had been five and a half hours in the hypertonic sea-water deprived of oxygen, about 90 per cent. segmented.

Let us consider one more illustration from Loeb's work in this field. Normally, in the forms with which he chiefly worked, sea-urchin, starfish, and certain molluscs, an absolutely essential condition for the continuation of life of the germ-cells after they are discharged from the body is that two cells, the ovum and the spermatozoon, shall unite in normal fertilization. Put in another way, parthenogenesis does not normally occur in these forms. Fertilization is an essential condition for the continuation of life and development. But Loeb's

painstaking and brilliant researches, extending over a number of years, show that when we say that fertilization is an essential condition for the continued life of the germ-cells outside the body, our language tends to obscure the most important fact, which is simply that for the continuation of life in these cells only certain internal physico-chemical conditions and adjustments must be realized. It makes no essential difference to the result whether these conditions are realized through the intervention of the sperm, as in normal fertilization, or by purely artificial chemical methods initiated, controlled and directed at every step by human agency. We can, in other words, regard all cases of successful artificial parthenogenesis as fundamentally a contribution to the physiology of natural death, and a demonstration of its essentially mechanistic basis. The conditions of continued existence are physical and chemical, and controllable as such. The methods finally worked out as optimum afford a complete demonstration of the thesis we have just stated. Thus, for example, the unfertilized egg of the sea-urchin, *Strongylocentrotus purpuratus*, will continue in life and develop perfectly normally if it is subjected to the following treatment: The eggs are first placed in sea-water to which a definite amount of weak solution of butyric acid has been added (50 cc. of sea-water + 2.8 c.c. n/10 butyric acid). In this solution at 15° C. the eggs are allowed to remain from 1½ to 3 or 4 minutes. They are then transferred to normal sea-water, in which they remain from 15 to 20 minutes. They are then transferred for 30 to 60 minutes at 15° C. to sea-water which has had its osmotic pressure raised by the addition of some salts (50 c.c. of sea-water+8 c.c. of 2½ m NaCl, or 2½ m NaCl+KCL+$CaCl_2$ in the proportion in which these

salts exist in sea-water). After the stay of from 30 to 60 minutes in this solution, the eggs are transferred back to normal sea-water, the transferring being in batches at intervals of 3 to 5 minutes between each batch transferred. It is then found that those eggs which have been just the right length of time in the hypertonic sea-water develop into perfectly normal sea-urchin larvæ. In other words, we have here a definite and known physico-chemical process completely replacing what was, before this work, universally regarded as a peculiarly vital process of extraordinary complexity, probably beyond power of human control.

These three examples from Loeb's work on the subject of prolongation of life in the egg cell will suffice for our present purposes. The lesson which they teach is plain, and is one which has, as will be readily perceived, a most important bearing upon the general concept of life and death outlined in the preceding chapter. The experiments demonstrate that the conditions essential to continued life of the germ-cells outside the body are physico-chemical conditions, and that when these cells die it is because the normal physico-chemical machinery for the continuation of life has either broken down, or has not been given the proper activating chemical conditions.

Lack of space alone prevents going in detail into another extremely interesting and important development of this subject, due to Dr. Frank R. Lillie of the University of Chicago. He has, in recent years made a thorough analysis of the biological factors operating when the egg of the sea-urchin is normally fertilized by a spermatozoon. The conception of the process of fertilization to which Lillie comes is "that a substance borne by the egg (fertilizin) exerts two kinds of actions: (1) an agglutin-

ating action on the spermatozoon and (2) an activating action on the egg. In other words, the spermatozoon is conceived, by means of a substance which it bears and which enters into union with the fertilizin of the egg, to release the activity of this substance within the egg.'' From the standpoint of the present discussion it is obvious that Lillie's results so far present nothing which in any way disturbs the conclusion we have reached as to the essentially physico-chemical nature of the processes which condition the continuation of life and development of the egg.

TISSUE CULTURE IN VITRO

Let us turn now to another question. Are the germ-cells the only cells of the metazoan body which possess the characteristic of potential immortality? There is now an abundance of evidence that such is not the case, but that, on the contrary, there are a number of cells and tissues of the body, which, under appropriate conditions, may continue living indefinitely, except for the purely accidental intervention of lethal circumstances. Every child knows that all the tissues do not die at the same time. It is proverbial that the tail of the snake, whose head and body have been battered and crushed until even the small boy is willing to admit that the job of killing is complete, ''will not die until the sun goes down.'' Galvani's famous experiment with the frog's legs only succeeded because some parts survive after the death of the organism as a whole. As Harrison points out ''Almost the whole of our knowledge of muscle-nerve physiology, and much of that of the action of the heart, is based upon experiments with surviving organs; and in surgery, where we have to do with changes involved in the repair of injured parts,

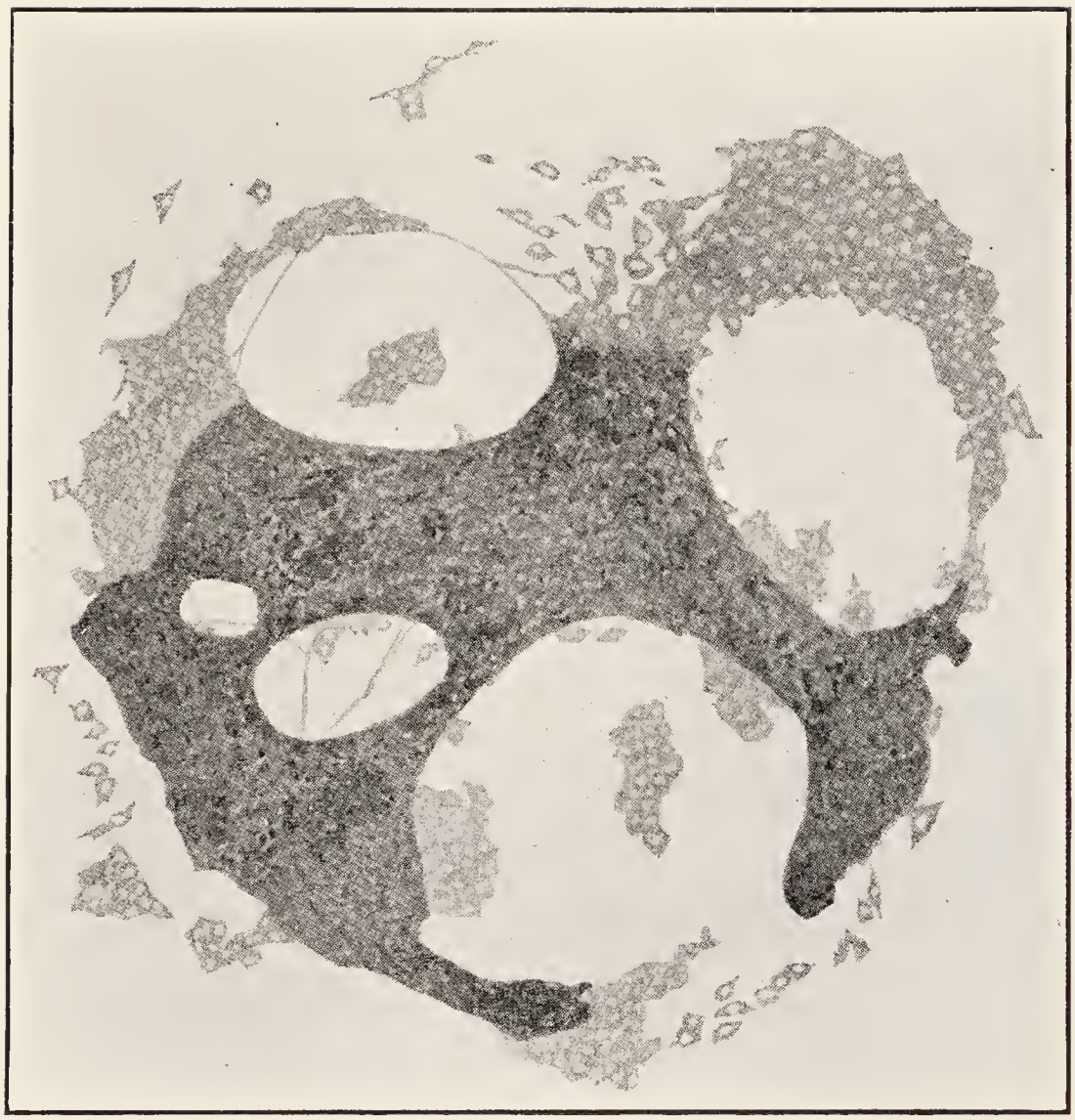


Fig. 13.—Piece of tissue from frog embryo cultivated in lymph, two days old. The dark portion shows original bit of tissue. Lighter portions are new growth. (From Harrison.)

FIG. 14.—Group of nerve fibers which have grown from an isolated piece of neural tube of a chick embryo. (From Harrison after Burrows.)

including processes of growth and differentiation, the power of survival of tissues and organs and their transplantability to strange regions, even to other individuals, has long formed the basis of practical procedures.''

The first successful cultures of somatic cells and tissues outside the body were those of Leo Loeb, described in 1897. His first method consisted in cultivating the tissues in appropriate media in test tubes. Later he used also another method, which involved the transplantation of the solid medium and the tissue into the body of another animal. What has been regarded as a defect of both these methods is that they do not permit the continued observation of the cells of the growing cultured tissue. To Harrison is due the development of a method which does permit such study. In 1907 he announced the discovery that if pieces of the developing nervous system of a frog embryo were removed from the body with fine needles, under strictly aseptic precautions, placed on a sterile cover slip in a drop of frog lymph, and the cover slip then inverted over a hollow glass slide, that the tissues would remain alive for many days, grow and exhibit remarkable transformations. By this technique it was possible to study the changes with a high power microscope and photograph them.

Figure 13 is a general view of one of these tissue cultures two days old. It shows a piece of nervous tissue from the frog embryo, with cells growing out from it into the lymph. The lighter portions are the new cells. In his remarkable monograph Harrison shows nerve cells developing fibers at first thickened, but presently becoming of normal character and size. At the ends are pseudopodial processes, by which the growing fiber attaches itself to the cover slip or other solid bodies. Fig-

ure 14 shows a particularly beautiful nerve fiber preparation made by Burrows.

The fibers grew from a preparation of the embryonic nervous system of the chick. There can be no doubt, as these figures so clearly show, of the life of these cells outside the body, or of the normality of their developmental and growth processes.

Under the guidance of Harrison, another worker, Burrows, improved the technique of the cultivation of tissues outside the body, first by using plasma from the blood instead of lymph and later in various other ways. He devised an apparatus for affording the tissue culture a continuous supply of fresh nutrient medium. There is in this apparatus a large culture chamber which takes the place of the plain hanging drop in an hermetically sealed cell. On the top of this culture chamber there is a wick, which carries the culture fluid from a supplying chamber and discharges it into a receiving chamber. The tissue is planted among the fibers of the wick, which are pulled apart where it crosses the top of the chamber. The whole system is kept sterile and so arranged that the growing tissue can be kept under observation with high powers of the microscope. The nutrient medium may be modified at will, and the effects of known substances upon the cellular activities of every sort may be studied.

Burrows began his investigations in this field on the tissues of the embryo chick. With the success of these cultures was established the fact that the tissues of a warm blooded animal were as capable of life, development, and growth outside the body as were those of cold-blooded animals, such as the frog. Burrows succeeded in cultivating outside the body, cells of the central nervous

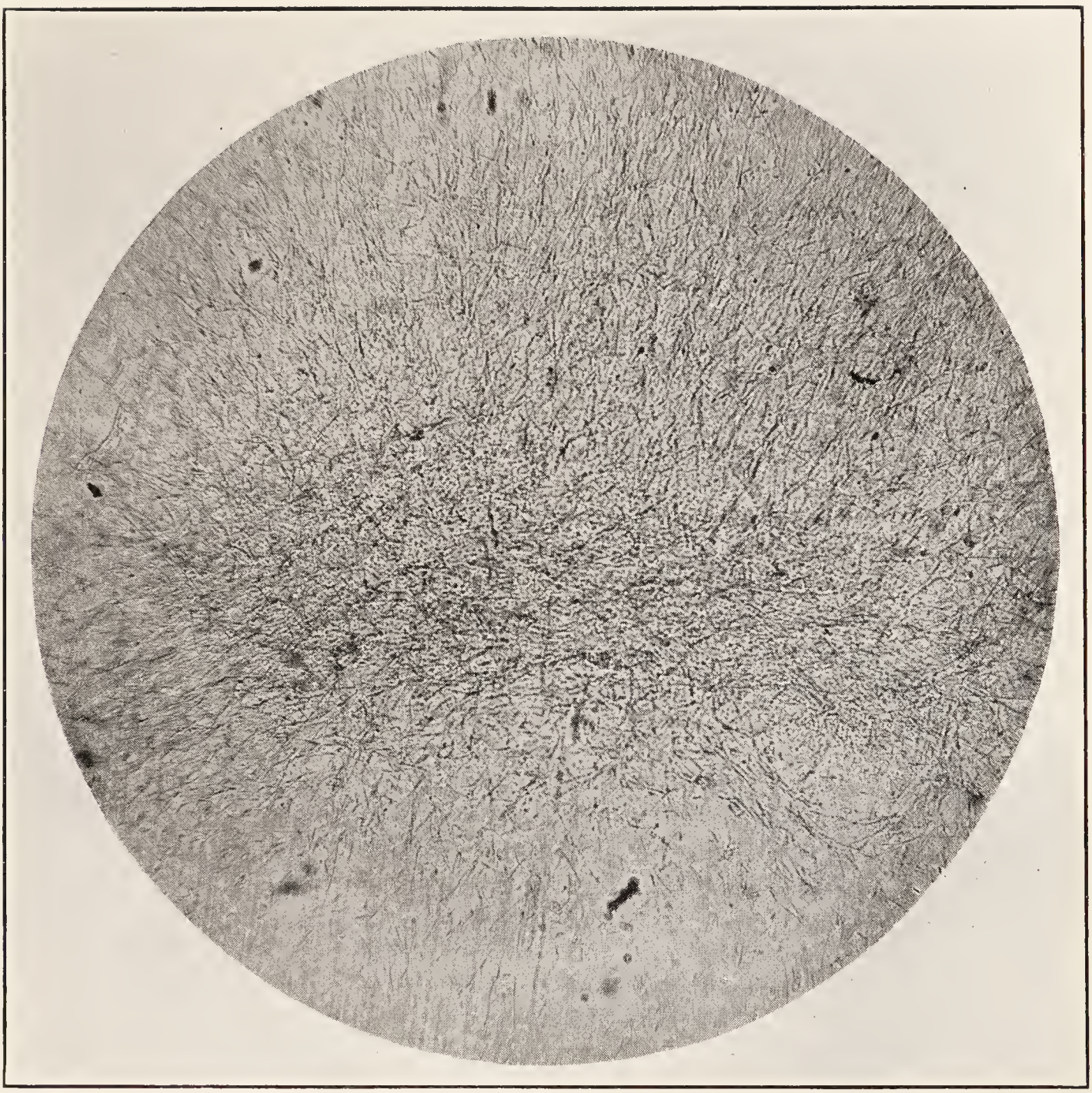


FIG. 15.—Human connective tissue cells fixed and stained with Giemsa stain. The culture was made by extirpating the central portion of culture 285 in its 16th passage, washing the remaining portion of the culture with Ringer solution without removing it from the cover-glass, and dropping on fresh plasm and extract. The preparation shows the extent of growth obtained in 48 hours from peripheral cells remaining after extirpation of the fragment. (After Losee and Ebeling.)

system, the heart, and mesenchymatous tissue of the chick embryo. At the same time Carrel was carrying on studies in this same direction at the Rockefeller Institute. In his laboratory were made the first successful cultures *in vitro* of the adult tissues of mammals. He developed a method of culture on a plate which permitted the growing of large quantities of material. He found that almost all the adult and embryonic tissues of dog, cat, chicken, rat, guinea pig, and man could be cultivated *in vitro*. Figure 15 shows a culture of human tissue, made at the Rockefeller Institute. I am indebted to Doctor Carrel and Doctor Ebeling for permission to present this photograph here.

According to the nature of the tissues cultivated, connective or epithelial cells were generated, which grew out into the plasma medium in continuous layers or radiating chains. Not only could normal tissues be cultivated but also the cells of pathological growths (cancer cells). It has been repeatedly demonstrated that normal cell division takes place in these tissues cultivated outside the body. The complex process of cell division, which is technically called mitosis, has been rightly regarded as one of the most characteristic, because complicated and unique, phenomena of normal life processes. Yet this process occurs with perfect normality in cells cultivated outside the body. Tissues from various organs of the body have been successfully cultivated, including the kidney, the spleen, the thyroid gland, etc. Burrows was even able to demonstrate that the isolated heart muscle cells of the chick embryo can divide as well as differentiate, and beat *rhythmically* in the culture medium.

Perhaps even more remarkable than the occurrence of such physiological activity as that of the heart muscle

cells *in vitro* is the fact that in certain lower forms of life a small bit of tissue or even a single cell, may develop in culture into a whole organism, demonstrating that the capacity of morphogenesis is retained in these isolated somatic cells. H. V. Wilson has shown that in coelenterates and sponges complete new individuals may develop *in vitro* from isolated cells taken from adult animals. By squeezing small bits of these animals through bolting cloth he was able to separate small groups of cells or even single cells. In culture these would grow into small masses of cells which would then differentiate slowly into the normal form of the complete organism. Figure 16 shows an example of this taken from Wilson's work.

It was early demonstrated by Carrel and Burrows that the life of the tissues *in vitro,* which varied in different experiments from 5 to 20 days, could be prolonged by a process of successive transfers of the culture to an indefinite period. Cells which were nearing the end of their life and growth in one culture need only be transferred to a new culture medium to keep on growing and multiplying. Dr. and Mrs. Warren H. Lewis made the important discovery that tissues of the chick embryo could be cultivated outside the body in purely inorganic solutions, such as sodium chloride, Ringer's solution, Locke's solution, etc. No growth in these inorganic cultures took place without sodium chloride. Growth was prolonged and increased by adding calcium and potassium. If maltose or dextrose, or protein cleavage products were added proliferation of the cells increased.

By the method of transfer to fresh nutrient media, Carrel has been able to keep cultures of tissue from the heart of the chick embryo alive for a long period of years. In a letter, recently received, he says: "The

Fig. 16.—Pennaria. Restitution mass six days old, completely metamorphosed, with developed hydranths. Op. perisarc of original mass; x, perisarc of outgrowth adherent to glass. (From Wilson.)

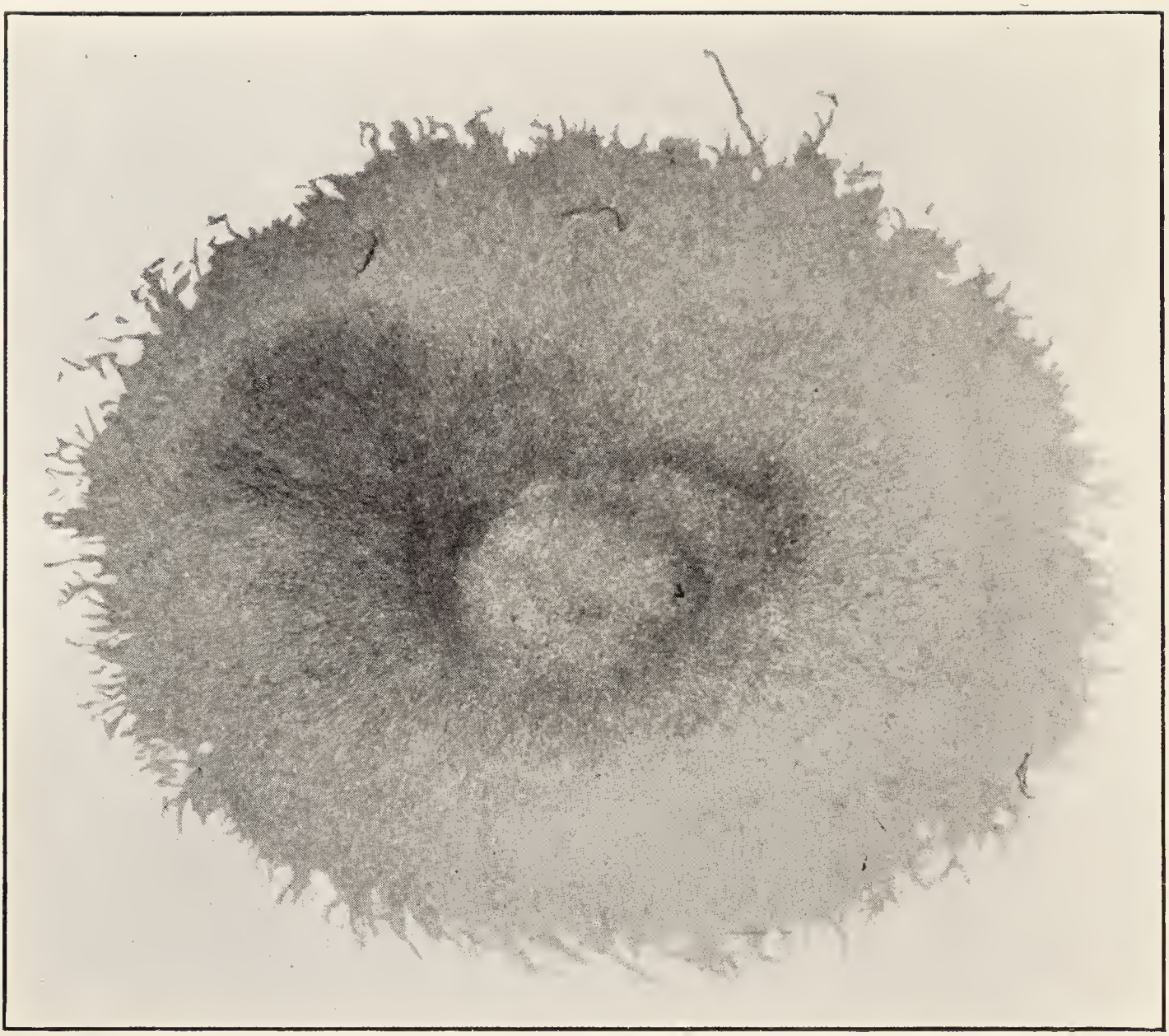


FIG. 17.—Culture of old strain of connective tissue. 1614 passage. 8 years and 8 months old, lacking 2 days. 48 hours' growth. x20. (Ebeling).

strain of connective tissue obtained from a piece of chick heart is still alive, and will be *nine years old* the seventeenth of January, 1921." Figure 17 is a photograph showing the present condition of this culture. It should be understood that this long continued culture has gone on at body temperature in an incubator, and not by keeping the culture at a low temperature and merely slowing down the vital processes.

This is indeed a remarkable result. It completes the demonstration of the potential immortality of somatic cells, when removed from the body to conditions which permit of their continued existence. Somatic cells have lived and are still living outside the body for a far longer time than the normal duration of life of the species from which they came. I think the present extent of Carrel's cultures in time fully disposes of Harrison's criticism to the effect that we are "not justified in referring to the cells as potentially immortal or even in speaking of the prolongation of life by artificial means, at least not until we are able to keep the cellular elements alive in cultures for a period exceeding the duration of life of the organism from which they are taken. There is at present no reason to suppose this cannot be done, but it simply has not been done as yet." I have had many years' experience with the domestic fowl, and have particularly studied its normal duration of life, and discussed the matter with competent observers of poultry. I am quite sure that for most breeds of domestic poultry the normal average expectation of life *at birth* is not substantially more than two years. For the longest lived races we know this normal average expectation of life cannot be over four years. I have never been able to keep a Barred Plymouth Rock alive more than seven

years. There are on record instances of fowls living to as many as 20 years of age. But these are wholly exceptional instances, unquestionably far rarer than the occurrence of centenarians among human beings. There can be no question that the nine years of life of Carrel's culture has removed whatever validity may have originally inhered in Harrison's point. And further the culture is just as vigorous in its growth today as it ever was, and gives every indication of being able to go on indefinitely, for 20 or 40, or any desired number of years.

The potential immortality of somatic cells has been logically just as fully demonstrated in another way as it has by these tissue cultures. Some nineteen years ago, Leo Loeb first announced the important discovery that potential immortality of somatic cells could be demonstrated through tumor transplantations. His latest summary of this work may well be quoted here:

"We must remember that common, transplantable tumors are the direct descendants of ordinary tissue cells, such as we normally find in the individuals of the particular species which we use. The tumors may be derived from a variety of normal tissues and, in general, the transformation from normal cells into tumor cells takes place under the influence of a long continued action of various factors enhancing growth. Tumor cells are, therefore, merely somatic cells which have gained an increased growth energy and at the same time somehow gained, in some cases, the power to escape the destructive consequences of homoiotoxins. This ability of certain tumors to grow in other individuals of the same species has enabled us to prove, through apparently endless propagation of these tumor cells in other individuals, that ordinary somatic cells possess potential immortality in the same sense in which protozoa and germ cells possess immortality. Thus tumor transplantation made possible the establishment of a fact of great biological interest, which, because of the homoiosensitiveness of normal tissues, could not be shown in the latter.

"We wish, however, especially to emphasize the fact that our experiments did not merely prove the immortality of tumor cells, but of the ordinary tissue cells as well, the large majority or all of which can be transformed into tumor cells. At an early stage of our investigations

we drew, therefore, on the basis of these experiments, the conclusion that ordinary tissue cells are potentially immortal; notwithstanding the fact that, especially under Weismann's influence, the opposite view had been generally accepted, and as it seems to us, with full justification, inasmuch as no facts were known at that time which suggested the immortality of somatic cells. It was the apparently endless transplantation of tumor cells which proved the contrary view.

"To recapitulate what we stated above: tumors are merely transformed tissue cells. All or the large majority of adult tissues are potential tumor cells. Tumor cells have been shown experimentally to be potentially immortal, therefore tissue cells are potentially immortal.

" This wider conclusion I expressed nineteen years ago. Quite recently, the immortality of certain connective tissue cells has been demonstrated by Carrel through *in vitro* culture of these cells. Under those conditions the tissue cells escape the mechanisms of attack to which the homoiotoxins expose the ordinary tissue cells in other individuals of the same species. Under these conditions the reactions of the host tissue against homoiotoxins which would have taken place *in vivo*, are eliminated. We must, however, keep in mind that this method of proving the immortality of somatic cells applies only to one particular, very favorable kind of cells; and it is very doubtful, if, by cultivation *in vitro*, the same proof could be equally well supplied in the case of other tissues. On the basis of tumor transplantations, on the contrary, we were able to show that a considerable variety, perhaps the large majority of all tissue cells possess potential immortality."

To Loeb unquestionably belongs the credit for first perceiving that death was not a necessary inherent consequence of life in the somatic cell, and demonstrating by actual experiments that somatic cells could, under certain conditions, go on living indefinitely.

Before turning to the next phase of our discussion, let us summarize the ground we have covered up to this point. We have seen that by appropriate control of conditions, it is possible to prolong the life of cells and tissues far beyond the limits of longevity to which they would attain if they remained in the multicellular body from which they came. This is true of a wide variety of cells and tissues differentiated in various ways. Indeed, the range of facts which have been ascertained

by experimental work in this field, probably warrants the conclusion that this potential longevity inheres in most of the different kinds of cells of the metazoan body, except those which are extremely differentiated for particular functions. To bring this potential immortality to actuality requires, of course, special conditions in each particular case. Many of these special conditions have already been discovered for particular tissues and particular animals. Doubtless, in the future many more will be worked out. We have furthermore seen that in certain cases the physico-chemical nature of the conditions necessary to insure the continuance of life has been definitely worked out and is well understood. Again this warrants the expectation that, with more extended and penetrating investigations in a field of research which is really just at its beginning, we shall understand the physics and chemistry of prolongation of life of cells and tissues in a great many cases where now we know nothing about it.

One further point and we shall have done with this phase of our discussion. The experimental culture of cells and tissues *in vitro* has now covered practically all the *essential* tissue elements of the metazoan body, even including the most highly differentiated of those tissues. Nerve cells, muscle cells, heart muscle cells, spleen cells, connective tissue cells, epithelial cells from various locations in the body, kidney cells, and others have all been successfully cultivated *in vitro*. We may fairly say, I believe, that the potential immortality of all essential cellular elements of the body either has been fully demonstrated, or else has been carried far enough to make the probability very great that properly conducted experiments would demonstrate the continuance of the

life of these cells in culture to any definite extent. It is not to be expected, of course, that such tissues as hair, or nails, would be capable of independent life, but these are essentially unimportant tissues in the animal economy as compared with those of the heart, the nervous system, the kidneys, etc. What I am leading to is the broad generalization, perhaps not completely demonstrated yet, but having regard to Leo Loeb's work, so near it as to make little risk inhere in predicting the final outcome, *that all the essential tissues of the metazoan body are potentially immortal.* The reason that they are not actually immortal, and that multicellular animals do not live forever, is that in the differentiation and specialization of function of cells and tissues in the body as a whole, any individual part does not find the conditions necessary for its continued existence. In the body any part is dependent for the necessities of its existence, as for example nutritive material, upon other parts, or put in another way, upon the organization of the body *as a whole. It is the differentiation and specialization of function of the mutually dependent aggregate of cells and tissues which constitute the metazoan body which brings about death, and not any inherent or inevitable mortal process in the individual cells themselves.*

An examination of different lines of evidence has led us to two general conclusions, *viz*:

a. That the individual cells and tissues of the body, in and by themselves, are potentially immortal.

b. That death of the metazoan body occurs, fundamentally, because of the way in which the cells and tissues are organized into a mutually dependent system.

Is there any further and direct evidence to be had

upon the second of these conclusions? So far our evidence in its favor has been indirect and inferential, though cogent so far as it goes. In this connection, a paper of Friedenthal's is of considerable interest. He shows that there is a marked correspondence between the longevity of various species of animals and a constant of organization which he calls the "cephalisation factor." This cephalisation factor in pure form, in his sense, is given by the equation.

$$\text{Cephalisation factor} = \frac{\text{Brain weight}}{\text{Total mass of body protoplasm.}}$$

Now "total mass of body *protoplasm*," as distinct from supporting structures, such as bone etc., is obviously difficult to determine directly. But Friedenthal is well convinced that, to a first approximation, the cephalisation factor may be written in this way:

$$\text{Cephalisation factor} = \frac{\text{Brain weight}}{(\text{Body weight})^{2/3}}$$

Computed upon the latter basis he sets up tables of the relation between cephalisation factor and longevity for mammals and for birds. It is not necessary to reproduce here the long tables, but to show the general point, the following table for five selected species of mammals will suffice:

TABLE 5

Relation between the cephalisation factor and longevity (Friedenthal)

Species	Cephalisation index	Duration of life
Mouse	0.045	6 years
Rabbit	.066	8 years
Marmoset (*Callithrix*)	.216	12 years
Deer	.35	15 years
Man	2.7	100 years

There appears in this short selected table a defect

which is even more apparent in his long ones, namely, that the figures for duration of life are distinctly round numbers. There is no evidence, for example, that the normal life span of the mouse is 6 years. All who have statistically studied the matter agree upon a much smaller figure than this. But, leaving this point aside, it is apparent that there is a parallelism of striking sort between the cephalisation factor and duration of life. In other words, it appears that the manner in which higher vertebrates, at least, are put together in respect of the proportionality of brain and body is markedly associated with the duration of life. It would be a matter of great interest to see whether this correlation between relative brain-weight and the expectation of life holds intra-racially as well as it does inter-racially. The bearing of these results of Friedenthal's upon our results as to the distribution of mortality upon a germ-layer basis, to be discussed in Chapter V *infra,* is obvious.

Another possible illustration of the general point now under discussion may be found in some recent work of Robertson and Ray. These authors, in a recent paper, have analyzed the growth curves of relatively long-lived mice as compared with the curves shown by relatively short-lived individuals. In the experiment both groups were subjected to the same kind of experimental treatment of various sorts, and the care with which the experiments were conducted in respect of control of the environmental factors renders the results highly interesting and valuable. The long-lived animals form a group which grows more rapidly in early life, and at the same time is less variable than the short lived group. The short-lived animals often grow much more rapidly in later life than the long-lived, but this accretion of tissue

was found to be relatively unstable. They further found that the long-lived animals represent a relatively stable group, highly resistant to external disturbing factors, and showing a more or less marked but not invariable tendency to early overgrowth and relative paucity of tissue accretion in late life. The short-lived animals are on the contrary relatively unstable, sensitive to external disturbing factors, and, as a rule, but not invariably, display relatively deficient early growth and a tendency to rapid accretion of tissue in later life.

In interpreting these results, Robertson and Ray believe that the differences are based upon the fact that in early or embryonic life the outstanding characteristic of the tissues is a high proportion of cellular elements, whereas in old age there is a marked increase in connective tissues. They further point out that connective tissue elements are ultimately dependent upon cellular tissues for their support, and that the connective tissues are expensive to maintain. They believe that the reason that the substance tethelin (*cf.* Chap. VII *infra*) prolongs life is because it accelerates the metabolism of the cellular elements to the detriment of the connective tissue elements. Longevity on this view is determined not by the absolute mass of living substance, but by the relative proportions of parenchymatous to sclerous tissues.

SENESCENCE

The facts presented in this and the preceding chapter clearly make it necessary to review with some care the current conception of senescence. Senescence, or growing old, is commonly considered to be the necessary prelude to "natural," as distinguished from accidental death.

But is the evidence really sound and complete that such is the fact?

A careful and unprejudiced examination will inevitably suggest to the open mind, I think, that much of the existing literature on senescence is really of no fundamental importance, because it has unwittingly reversed the true sequential order of the causal nexus. If cells of nearly every sort are capable, under appropriate conditions, of living indefinitely in undiminished vigor, and cytological normality, there is little ground for postulating that the observed senescent changes in these cells while in the body, such as those described by Minot and others, are expressive of specific and inherent mortal processes going on in the cells; or that these cellular processes are the cause of senescence, as Minot has concluded.

That there is such a phenomenon as senescence is, of course, certain. It is observable both in *Protozoa* and in *Metazoa*. The real question, however, is a twofold one, *viz*: (a) is senescence in either Protozoa or Metazoa an *inevitable consequence* of the strain or the individual having lived; and (b) is senescence a *necessary* associate and forerunner of natural death?

Let us briefly reconsider the facts. In Protozoa a slowing down of the division rate in culture has been frequently observed; and it has been held, first, that this is a phenomenon essentially homologous to senescence in the metazoan; and second, that if nuclear reorganization, by the way either of endomixis or of conjugation, did not occur that the strain would die out. Indeed, Jennings, in discussing the matter in his last book says:

> "Thus it appears that in these organisms nature has employed the method of keeping on hand a reserve stock of a material essential to

life; by replacing at intervals the worn out material with this reserve, the animals are kept in a state of perpetual vigor; not, as individuals, growing old or dying a natural death. Nevertheless, a wearing out process, such as might be called getting old, does occur in the structures employed in the active functions of life, and these must be replaced after a time of service. So far as the conditions in these organisms are typical, deterioration and death do appear to be a consequence of full and active life; life carries within itself the seeds of death. It is not mating with another individual that avoids this end; but replacement of the worn material by a reserve.....The great mass of cells subject to death in the higher animals dwindles in the infusorian to the macronucleus; this alone represents a corpse. But the dissolution of this corpse occurs within the living body. It much resembles such a process as the wasting away and destruction of minute parts of our own bodies, which we know is taking place at all times, and which does not interrupt the life of the individual."

It is doubtful if this position is warranted. Since Jennings wrote the statement quoted, some new and pertinent data have appeared in regard to amicronucleate infusoria. Woodruff and his co-workers have shown that such races may occur rather commonly. Thus Woodruff, in 1921, says:

"During the past year, the isolation for certain experiments of 14 "wild" lines representing 6 species of hypotrichous ciliates revealed 7 lines (4 species) with micronuclei and 7 lines (2 species) without morphological micronuclei. Ten of the lines were all isolated from a "wild" mass culture of the same species *Urostyla grandis*, found in a laboratory aquarium. Six of these lines were amicronucleate. All of the lines of all of the species have bred true with respect to the character in question, and one amicronucleate line at present is at the 102d generation.

Similarly a culture of *Paramecium caudatum*, which the present writer supplied a year ago to a course in protozoölogy for the study of the nucleus, failed to reveal a micronucleus, although in other races the micronucleus was readily demonstrated."

Now, since it is the micronucleus which furnishes for the process of endomixis the "reserve stock of a material essential to life" which Jennings discusses, it is plain that the existence of amicronucleate races of Protozoa

at once puts a new face upon the whole matter. Dawson has studied in continued culture one of these amicronucleate races of *Oxytricha hymenostoma* Stokes. His conclusion is as follows:

"The existence of a form which not only apparently may live indefinitely without conjugation, autogamy, or endomixis (assuming the possibility of the latter phenomenon in an hypotrichous form), but also apparently does not possess the ability to undergo any of these phenomena, brings to light an entirely new possibility in the life history of ciliates. It has been proved quite conclusively, (Woodruff, '14), that in forms which ordinarily conjugate, the continued prevention of this process brings about no loss of viability if a favorable environment be provided. However, in the organism under consideration there is apparently no possibility not only of conjugation or endomixis, but also of autogamy; and thus we have from another source crucial evidence that none of these phenomena is an indispensable factor in the life-history of this hypotrichous form."

In the light of these clean cut and definite results one is more disposed than was formerly the case to accept at their face value the results of Enriques with *Glaucoma pyriformis,* and those of Hartmann with *Eudorina elegans,* in which reproduction went on indefinitely with undiminished vigor and no evidence of any process comparable to endomixis.

Altogether, it seems to me that the weight of the evidence now is that in the Protozoa, senescence (or death), is not a *necessary or inevitable consequence* of life. Given the appropriate and necessary conditions of environment, true immortality—the absence of both senescence and natural death, each defined in the most critical manner—is in fact the reality for a number of forms.

Turning to the metazoan side of the case, the evidence regarding senescence is equally cogent. In the first place, in the longest continued *in vitro* tissue cultures known (those of Carrel) there is, as already stated, no appear-

ance of senescence in the cells. But it may be objected that an element of uncertainty is injected into the case, by the fact that, as Carrel and Ebeling have lately discussed in some detail, it has been necessary in carrying along this long-continued culture to add regularly to the culture medium a small amount of "embryonic juice." One might urge that, but for the "embryonic juice," cellular senescence and death would have appeared. But suppose this to be granted fully. It does not mean that senescence is a necessary and inevitable consequence of life, but only that to realize a potential immortality the cells must have an appropriate environment, one element of which is presumably some chemical combination which, so far, one has supplied only through "embryonic juice."

An entirely different sort of evidence and one of great significance is found in the facts of clonal propagation of plants, well known to horticulturists. An individual apple tree grows old, and eventually dies, as a tree. But at all periods of its life, including all stages of senescence up to the terminal one, death, it produces shoots each spring. If one of these shoots is grafted to another root, it will, in the passage of time, make first a young tree, then a middle aged tree, and finally an old, senescent tree; which, in turn, will make new shoots, which may, in turn, be grafted to new roots, and so on *ad infinitum*. It is not even absolutely necessary that the shoot be grafted to a new root; though, of course, this is the manner in which the great majority of our orchards are, in fact, propagated, and have been since the beginning of horticultural history. Anyone who is familiar with the woods of New England, not too far from settlements, has seen apple trees in the woods where a

shoot, whose continuity with the base of its parent tree has never been broken, makes a new tree after the old one has died—indeed in some cases the shoot has helped the mortiferous process by the vigorous crowding of youth. In this whole picture how fares any idea of the *necessity* or *inevitableness* of cellular (somatic) senescence? Such an idea plainly has no place in the realities of the continued existence of apple trees.

From these facts it is a logically cogent induction to infer that when cells show the characteristic senescent changes which were discussed in the preceding chapter, it is because they are reflecting in their morphology and physiology a consequence of their mutually dependent association in the body as a whole, and not any necessary progressive process inherent in themselves. In other words, may we not tentatively, in the light of our present knowledge, regard *senescence as a phenomenon appearing in the multicellular body as a whole,* as a result of the fact that it is a differentiated and conferentiated (to employ a useful term lately introduced by Ritter) *morphologic and dynamic organization.* This phenomenon is reflected morphologically in the component cells. But it does not primarily originate in any particular cell because of the fact that that cell is old in time, or because that cell in and of itself has been alive; nor does it occur in the cells when they are removed from the mutually dependent relationship of the organized body as a whole and given appropriate physico-chemical conditions. In short, senescence appears not to be a primary attribute of the physiological economy of cells as such.

If this conception of the phenomenon of senescence is correct in its main features, it suggests the essential futility of attempting to investigate its causes by purely

cytological methods. On the other hand, by clearing away the unessential elements, it indicates where research into the problem of causation of senescence may be profitable.

An extremely interesting contribution to the problem of senescence has been made by Carrel and Ebeling in their most recent paper, in which they show that the rate of multiplication of fibroblasts *in vitro*, and the duration of life of such cultures, is inversely proportional to the age of the animal from which the serum for the culture medium is taken. These results are of such considerable interest that it will be well to quote in full the summary of them given by the authors:

"Pure cultures of fibroblasts displayed marked differences in their activity in the plasma of young, middle aged, and old chickens. The rate of cell multiplication varied in inverse ratio to the age of the animal from which the plasma was taken. There was a definite relation between the age of the animal and the amount of new tissue produced in its plasma in a given time. The chart obtained by plotting the rate of cell proliferation in ordinates, and the age of the animal in abscissæ, showed that the rate of growth decreased more quickly than the age increased. The decrease in the rate of growth was 50 per cent. during the first 3 years of life, while in the following 6 years it was only 30 per cent. When the duration of the life of the cultures in the four plasmas was compared, a curve was obtained which showed about the same characteristics. The duration of life of the fibroblasts *in vitro* varied in inverse ratio to the age of the animal, and decreased more quickly than the age increased.

"As the differences in the amount of new tissue produced in the plasma of young, middle aged, and old chickens were large, the growth of a pure culture of fibroblasts could be employed as a reagent for detecting certain changes occurring in the plasma under the influence of age.

"A comparative study of the growth of fibroblasts in media containing no serum, and serum under low and high concentrations was made, in order to ascertain whether the decreasing rate of cell multiplication was due to the loss of an accelerating factor, or to the increase of an inhibiting one. In high and low concentrations of the serum of young animals, no difference in the rate of multiplication of fibroblasts was observed. This showed that the serum of an actively growing animal did not contain any accel-

erating agent. The same experiments were repeated with the serum of a 3 year old and a 9 year old chicken. The medium made of a high concentration of serum had a markedly depressing effect on the growth, and this effect was greater in the serum of the older animal.

"The results of the experiments showed in a very definite manner that certain changes occurring in the serum during the course of life can be detected by modifications in the rate of growth of pure cultures of fibroblasts and that these changes are characterized by the increase of an inhibiting factor, and not by the loss of an accelerating one. It appeared, therefore, that the substances which greatly accelerate the multiplication of fibroblasts and are found in the tissues do not exist in the blood serum, or are constantly shielded by more active inhibiting factors. The curve which expresses the variations of the inhibiting factor in function of the age was compared with that showing the variations of the rate of healing of a wound according to the age of the subject. For wounds of equal size, the index of cicatrization, which expresses the rate of healing, varies in inverse ratio to the age. The different values of the index of cicatrization of a wound 40 sq. cm. in area, taken from measurements made by du Noüy, were plotted in ordinates, and the age of the subject in abscissæ. The curve showed a decrease in the activity of cicatrization, which resembled the decrease in the rate of growth of fibroblasts in function of the age of the animal. This suggested the existence of a relation between the factors determining both phenomena."

These results suggest that there is produced in some cases by the body or some of its parts, a substance which inhibits the power of cells to multiply or to remain alive. How general such a phenomenon is in occurrence does not yet appear, but, apparently, it must be absent in the case of clonal reproduction in plants already discussed, and in the analogous case of agamic reproduction in lower *Metazoa* (*cf.* planarians). It seems possible that the results of Carrel and Ebeling might be open to a slightly different interpretation than that which they give, which hypothecates a specific inhibiting substance in the serum, increasing in either amount or specific potency with age. It seems to me that all of their facts could be interpreted with equal cogency on the supposition that the serum from an old animal is itself senes-

cent as a whole; that is, has undergone a physico-chemical alteration (as compared with that of a young animal), which is comparable to the morphological and physiological changes which are observable in senescent cells. It may further quite reasonably be supposed that "senescent" serum, because of these physico-chemical alterations, does not furnish so favorable a nutrient medium for *in vitro* cultures as does "young" serum. Such a view avoids the necessity of postulating a specific "senescent" substance, the existence of which would be exceedingly difficult to prove.

But in any case, whatever explanation is suggested for Carrel and Ebeling's brilliant results, it does not seem to me that the results themselves, which alone are the realities pertinent in the premises, either offer any obstacle to or, indeed, alter the interpretation of senescence which I have suggested above. For, what the results really demonstrate is, essentially, that the serum of old animals is a less favorable component of the nutrient medium of cells *in vitro* than is the serum of young animals. This fact is a contribution to our knowledge of the phenomena and attributes of senescence of first-class importance; but it does not *per se,* as it appears to me, permit of any new generalization as to the etiology of senescence.

CHAPTER III

THE CHANCES OF DEATH

THE LIFE TABLE

Up to this point in our discussion of death and longevity we have, for the most part, dealt with general and qualitative matters, and have not made any particular examination as to the quantitative aspects of the problem of longevity. To this phase attention may now be directed. For one organism, and one organism only, do we know much about the quantitative aspects of longevity. I refer, of course, to man, and the abundant records which exist as to the duration of his life under various conditions and circumstances. In 1532 there began in London the first definitely known compilation of weekly "Bills of Mortality." Seven years later, the official registration of baptisms, marriages and deaths was begun in France, and shortly after the opening of the seventeenth century similar registration was begun in Sweden. In 1662 was published the first edition of a remarkable book, a book which marks the beginning of the subject which we now know as "vital statistics." I refer to "Natural and Political Observations Mentioned in the Following Index, and made upon the Bills of Mortality" by Captain John Graunt, Citizen of London. From that day to this, in an ever widening portion of the inhabited globe we have had more or less continuous published records about the duration of life of man. The amount of such material which has accumulated is enormous. We are only at the

beginning, however, of its proper mathematical and biological analysis. If biologists had been furnished with data of anything like the same quantity and quality for any other organism than man it is probable that a vastly greater amount of attention would have been devoted to them than ever has been given to vital statistics, so-called, and there would have been as a result many fundamental advances in biological knowledge now lacking, because material of this sort so generally seems to the professional biologist to be something about which he is in no way concerned.

Let us examine some of the general facts about the normal duration of life in man. We may put the matter in this way: Suppose we started out at a given instant of time with a hundred thousand infants, equally distributed as to sex, and all born at the same instant of time. How many of these individuals would die in each succeeding year, and what would be the general picture of the changes in this cohort with the passage of time? The facts on this point for the Registration Area of the United States in 1910 are exhibited in Figure 18, which is based on Glover's United States Life Tables.

In this table are seen two curved lines, one marked l_x and the other d_x. The l_x line indicates the number of individuals, out of the original 100,000 starting together at birth, who survived at the beginning of each year of the life span, indicated along the bottom of the diagram. The d_x line shows the number dying within each year of the life span. In other words, if we subtract the number dying within each year from the number surviving at the beginning of that year we shall get the series of figures plotted as the l_x line. We note that in the very first year of life the original hundred thousand lose over

one-tenth of their number, there being only 88,538 surviving at the beginning of the second year of life. In the next year 2,446 drop out, and in the year following that 1,062. Then the line of survivors drops off more slowly between the period of youth and early adult life. At 40 years of age, almost exactly 30,000 of the original 100,000 have passed away, and from that point on the l_x line descends with ever increasing rapidity, until about

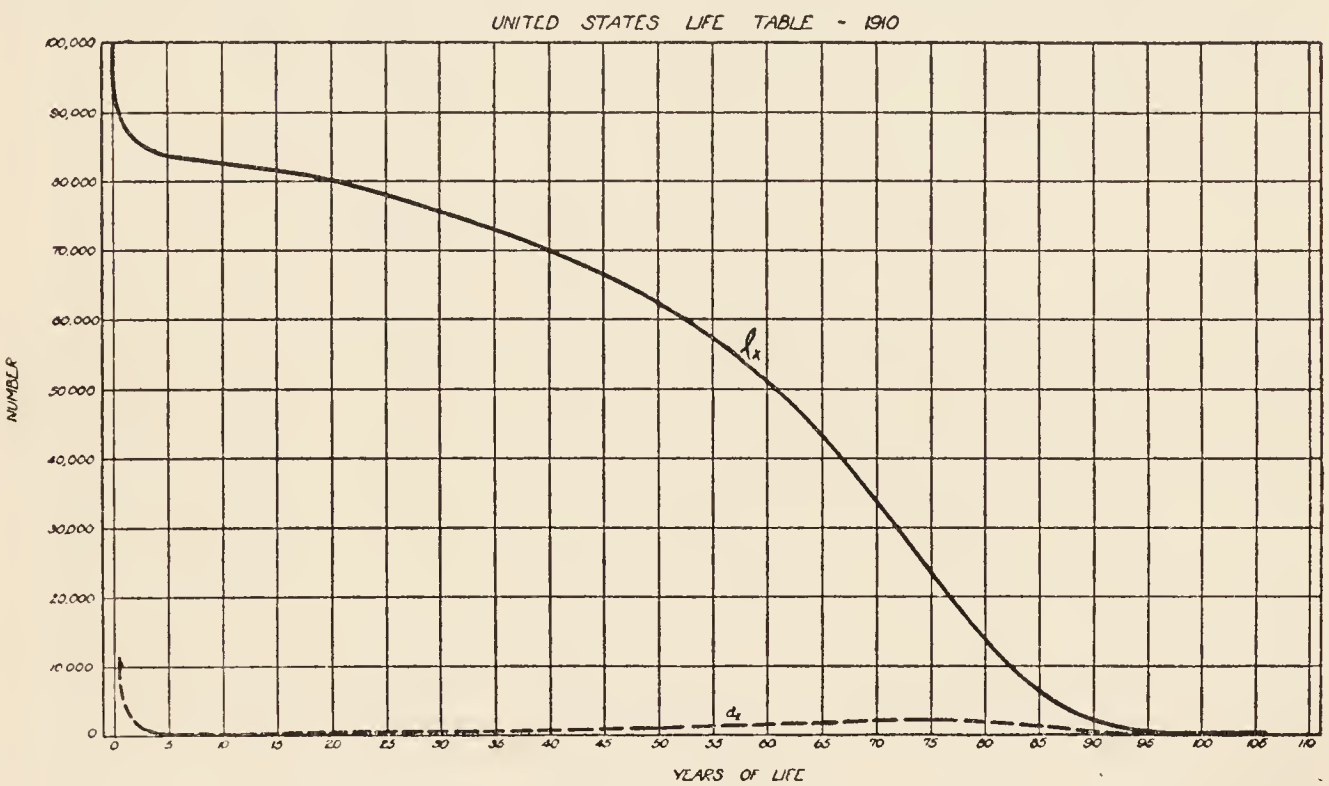


FIG. 18.—Life table diagram. For explanation see text.

age 80, when it once more begins to drop more slowly, and the last few survivors pass out gradually, a few each year until something over the century mark is reached, when the last one of the 100,000 who started across the bridge of life together will have ended his journey.

This diagram is a graphic representation of that important type of document known as a life or mortality table. It puts the facts of mortality and longevity in their best form for comparative purposes. The first such table actually to be computed in anything like the modern fashion was made by the astronomer, Dr. E. Halley, and

was published in 1693, although thirty years before that time Pascal and Fermat (*cf.* Levasseur) had laid down certain mathematical rules for the calculation of the probabilities of human life. Since Halley's time a great number of such tables have been calculated. Dawson fills a stout octavo volume with a collection of the more important of such tables, computed for different countries and different groups of the population. Now they have become such a commonplace that elementary classes in vital statistics are required to compute them (see for example Dublin's New Haven life table).

CHANGES IN EXPECTATION OF LIFE

I wish to pass in graphic review some of these life tables in order to call attention in vivid form to an important fact about the duration of human life. In order to bring out the point with which we are here concerned it will be necessary to make use of another function of the mortality table than either the l or d_x lines which are shown in Figure 18. I wish to discuss expectation of life at each age. The expectation of life at any age is defined in actuarial science as the mean or average number of years of survival of persons alive at the stated age. It is got by dividing the total survivor-years of after life by the number surviving at the stated age. Or, if we let e_x denote what is called the curtate expectation of life

$$e_x = \frac{l_x + l_{x+1} + l_{x+2} + \ldots\ldots\ldots + l_{x+n}}{l_x}$$

To a first approximation, sufficiently accurate for our present purposes, the total expectation of life, called $\mathring{e}_x$, may be obtained from the curtate expectation by the simple relation

$$\mathring{e}_x = e_x + 1/2$$

TABLE 6

Changes in expectation of life from the seventeenth century to the present time

Age	Average length of life remaining to each one alive at beginning of age interval			Age	Average length of life remaining to each one alive at beginning of age interval		
	Breslau, 17th century	Carlisle, 18th century	U.S. 1910		Breslau, 17th century	Carlisle, 18th century	U.S. 1910
0– 1	33.50	38.72	51.49	50– 51	16.81	21.11	20.98
1– 2	38.10	44.67	57.11	51– 52	16.36	20.39	20.28
2– 3	39.78	47.55	57.72	52– 53	15.92	19.68	19.58
3– 4	40.75	49.81	57.44	53– 54	15.48	18.97	18.89
4– 5	41.25	50.76	56.89	54– 55	14.99	18.27	18.21
5– 6	41.55	51.24	56.21	55– 56	14.51	17.58	17.55
6– 7	41.62	51.16	55.47	56– 57	14.02	16.89	16.90
7– 8	41.16	50.79	54.69	57– 58	13.54	16.21	16.26
8– 9	40.95	50.24	53.87	58– 59	13.06	15.55	15.64
9–10	40.50	49.57	53.02	59– 60	12.57	14.92	15.03
10–11	39.99	48.82	52.15	60– 61	12.09	14.34	14.42
11–12	39.43	48.04	51.26	61– 62	11.62	13.82	13.83
12–13	38.79	47.27	50.37	62– 63	11.14	13.31	13.26
13–14	38.16	46.50	49.49	63– 64	10.67	12.81	12.69
14–15	37.51	45.74	48.60	64– 65	10.20	12.30	12.14
15–16	36.86	44.99	47.73	65– 66	9.73	11.79	11.60
16–17	36.22	44.27	46.86	66– 67	9.27	11.27	11.08
17–18	35.57	43.57	46.01	67– 68	8.81	10.75	10.57
18–19	34.92	42.87	45.17	68– 69	8.36	10.23	10.07
19–20	34.26	42.16	44.34	69– 70	7.91	9.70	9.58
20–21	33.61	41.46	43.53	70– 71	7.53	9.17	9.11
21–22	32.95	40.75	42.73	71– 72	7.17	8.65	8.66
22–23	32.34	40.03	41.94	72– 73	6.85	8.16	8.22
23–24	31.67	39.31	41.16	73– 74	6.56	7.72	7.79
24–25	31.00	38.58	40.38	74– 75	6.25	7.33	7.38
25–26	30.38	37.86	39.60	75– 76	5.99	7.00	6.99
26–27	29.76	37.13	38.81	76– 77	5.79	6.69	6.61
27–28	29.14	36.40	38.03	77– 78	5.71	6.40	6.25
28–29	28.51	35.68	37.25	78– 79	5.66	6.11	5.90
29–30	27.93	34.99	36.48	79– 80	5.67	5.80	5.56
30–31	27.35	34.34	35.70	80– 81	5.74	5.51	5.25
31–32	26.76	33.68	34.93	81– 82	5.86	5.20	4.96
32–33	26.18	33.02	34.17	82– 83	6.02	4.93	4.70
33–34	25.59	32.36	33.41	83– 84	5.85	4.65	4.45
34–35	25.05	31.68	32.66	84– 85		4.39	4.22
35–36	24.51	31.00	31.90	85– 86		4.12	4.00
36–37	23.97	30.32	31.16	86– 87		3.90	3.79
37–38	23.43	29.63	30.42	87– 88		3.71	3.58
38–39	22.88	28.95	29.68	88– 89		3.59	3.39
39–40	22.33	28.27	28.94	89– 90		3.47	3.20
40–41	21.78	27.61	28.20	90– 91		3.28	3.03
41–42	21.23	26.97	27.46	91– 92		3.26	2.87
42–43	20.73	26.33	26.73	92– 93		3.37	2.73
43–44	20.23	25.71	25.99	93– 94		3.48	2.59
44–45	19.72	25.08	25.26	94– 95		3.53	2.47
45–46	19.22	24.45	24.54	95– 96		3.53	2.35
46–47	18.72	23.81	23.82	96– 97		3.46	2.24
47–48	18.21	23.16	23.10	97– 98		3.28	2.14
48–49	17.71	22.50	22.39	98– 99		3.07	2.04
49–50	17.25	21.81	21.69	99–100		2.77	1.95

In each of the series of diagrams which follow there is plotted the approximate value of the expectation of

life for some group of people at some period in the more or less remote past, and for comparison the expectation of life, either from Glover's table, for the population of the United States Registration Area in 1910—the expectation of life of our people now, in short—or equivalent figures for a modern English or French population.

Because of the considerable interest of the matter, and the fact that the data are not easily available to

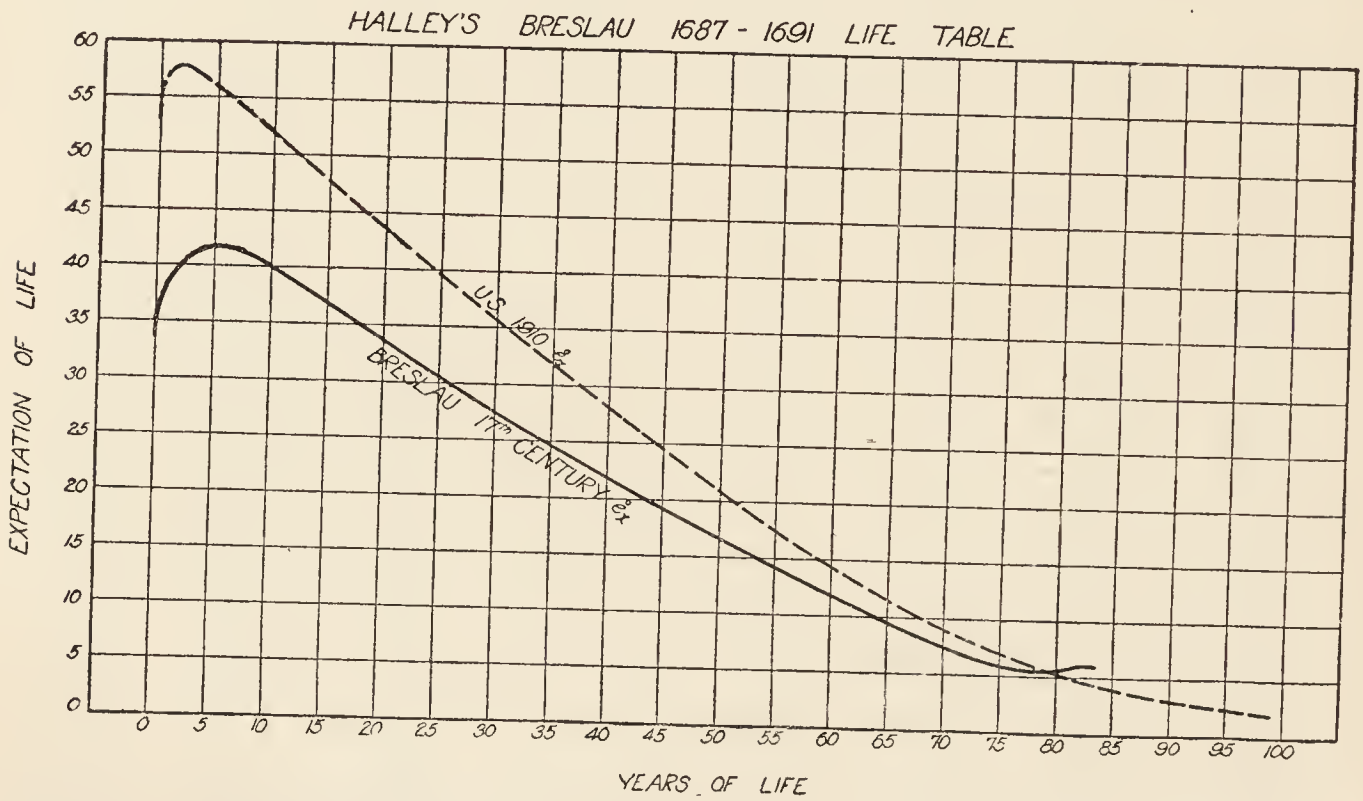


FIG. 19.—Comparing the expectation of life in the 17th century with that of the present time.

biologists, Table 6 is inserted, giving the expectations of life from which certain of the diagrams have been plotted.

Figure 19 gives the results from Halley's table, based upon the mortality experience in the city of Breslau, in Silesia, during the years 1687 to 1691. This gives us a rough, but in its general sweep sufficiently accurate picture of the forces of mortality towards the end of the seventeenth century From this diagram it appears that at birth the expectation of life of an individual born in Breslau in the seventeenth century was much lower than

that of an individual born in the United States in 1910. The difference amounts to approximately 18 years! Probably the actual difference was not so great as this, as these early life tables are known to be inaccurate at the ends of the lifespan, particularly at the beginning. At 10 years of age, the difference in expectation of life had been reduced to just over 12 years; at age 20, to a little less than 10 years; at age 30 to 7-⅓ years; at age 50 to just over 4 years; at age 70 to 1-½ years. At age 80 the lines have crossed, but owing to the inadequate methods of graduation used by this pioneer actuary, together with the paucity and probably somewhat inaccurate character of his material, no stress is to be laid upon the crossing of the lines, or upon the superior expectation of life at the high ages in the seventeenth century material. What the diagram shows is that the expectation of life at early ages was vastly inferior in the seventeenth century to what it is now, while at advanced ages the chances of living were substantially the same. Let us defer the further discussion of the meaning and explanation of this curious fact until we have examined some further data.

Figure 20 compares the expectation of life in England at the middle of the eighteenth century, or about a century later than the last, with present conditions in the United States. Again we see that the expectation at birth was greatly inferior then to what it is now, but the difference is not so great as it was a century earlier, amounting to but 12-¾ years instead of the 18 we found before. Further it is seen that, just as before, the expectations come closer together with advancing age. By the time age 45—middle life—is reached the expectation of life was substantially the same in the eighteenth cen-

tury as it is now. At age 47 the eighteenth century line crosses that for the twentieth century, and with a few trifling exceptions, notably in the years from 56 to 62, the expectation of life for all higher ages was greater then than it is now. We see in the eighteenth century the same *kind* of result as was indicated in the seventeenth, only differing in degree.

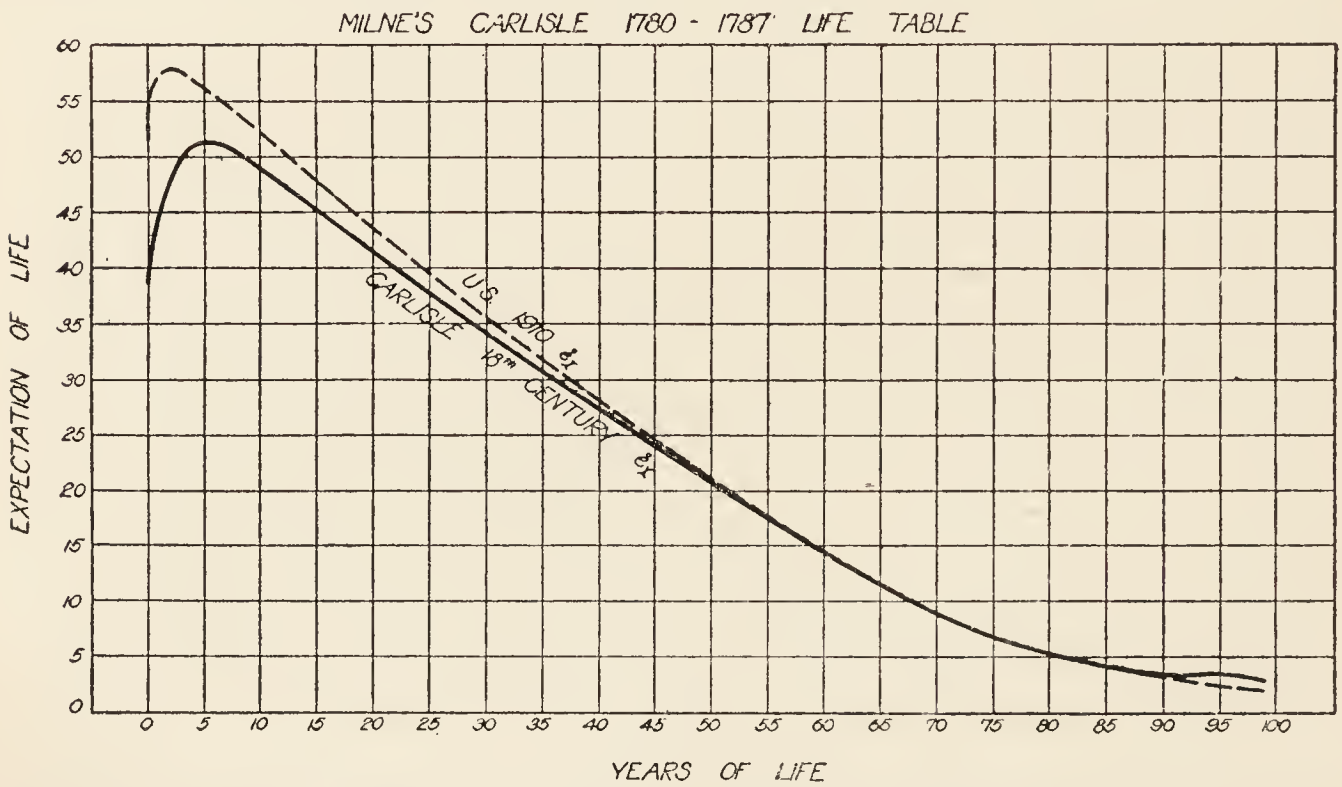


Fig. 20—Comparing the expectation of life in the 18th century with that of the present time.

It should be noted that all data as to mortality in the seventeenth and eighteenth centuries lack the degree of accuracy which one desires for purely scientific purposes. By erring generally on the safe side these old mortality tables did well enough for insurance purposes. But quite different results as to the detailed values of life table constants in these early periods are to be found in the literature. For example, Richards constructed some life tables from New England genealogical records, and compared them with Wigglesworth's table, and also with those of modern times. His general conclusion, for the

New England population, is: "that during the last half-century longevity* in Massachusetts, and probably in New England, has increased, that from 1793 to 1850 the increase is less certain and from the seventeenth to the eighteenth century what data we have point rather to a decrease than to anything else." This result may mean any one of a number of things. It may mean merely inadequate and inaccurate data on which the seventeenth century tables were calculated. It may mean a result of less stringent selection in the makeup of the population with the passage of time. In any case it applies only to a small and rather homogeneous group of people.

The changes in expectation of life from the middle of the seventeenth century to the present time where the records are most extensive and reliable appear to furnish a record of a real evolutionary progression. In this respect at least man has definitely and distinctively changed, as a race, in a period of three and a half centuries. This is, of course, a matter of extraordinary interest, and at once stimulates the desire to go still farther back in history and see what the expectation of life then was. Fortunately, through the labors of Karl Pearson, and his associate, W. R. Macdonell, it is possible to do this, if not with precise accuracy, at least to a rough first approximation. Pearson has analyzed the records as to age at death which were found upon mummy cases studied by Professor W. Spiegelberg. These mummies belonged to a period between 1,900 and 2,000 years ago, when Egypt was under Roman dominion. The data were extremely meagre, but from Pearson's analysis of them it has been possible to

* Richards somewhat loosely uses this term when he means "expectation of life."

construct the diagram which is shown in Figure 21. Each circle marks a point where it was possible definitely to calculate an expectation of life. The curve running through the circles is a rough graphic smoothing of the scattered observed data. Unfortunately, there were no records of deaths in early infancy. Either there were no baby mummies, or if there were they have disappeared.

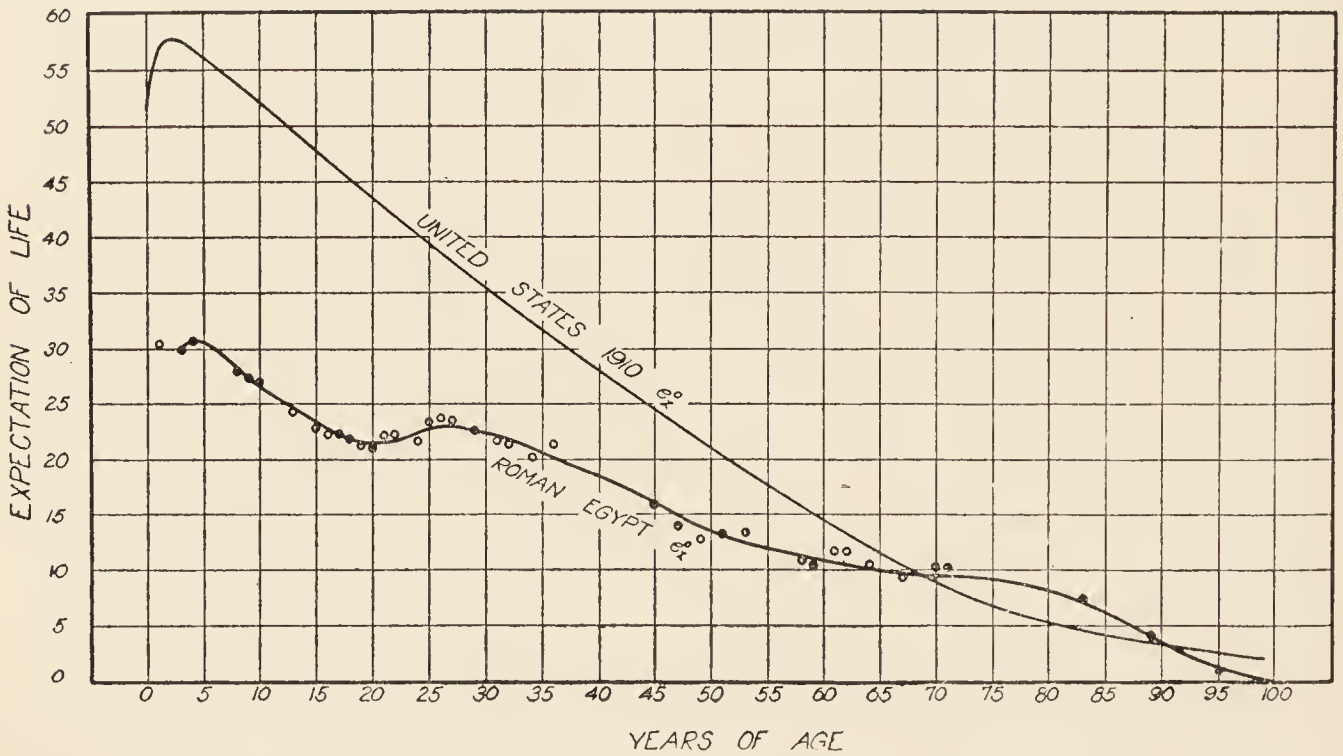


FIG. 21.—Comparing the expectation of life of Ancient Egyptians with that of present day Americans. Plotted from Pearson's and Glover's data.

For comparison, the expectation of life from Glover's 1910 United States life table is inserted.

It will be seen at once that the general sweep of the line is of the same sort that we have already observed in the case of the seventeenth century table. In the early years of life the expectation was far below that of the present time, but somewhere between ages 65 and 70 the Egyptian line crosses the modern American line, and from that period on the individuals living in Egypt at about the time of the birth of Christ could apparently look forward to a longer remaining duration of life, on the aver-

age, than can the American of the present day. Pearson's comment on this fact is worth quoting. He says: "In the course of those centuries man must have grown remarkably fitter to his environment, or else he must have fitted his environment immeasurably better to himself. No civilized community of to-day could show such a curve as the civilized Romano-Egyptians of 2,000 years ago exhibit. We have here either a strong argument for the survival of the physically fitter man or for the survival of the civilly fitter society. Either man is constitutionally fitter to survive to-day, or he is mentally fitter, *i.e.*, better able to organize his civic surroundings. Both conclusions point perfectly definitely to an evolutionary progress. . . . That the expectation of life for a Romano-Egyptian over 68 was greater than for a modern English man or woman is what we might expect, for with the mortality of youth and of middle age enormously emphasized only the very strongest would survive to this age. Out of 100 English alive at 10 years of age 39 survive to be 68; out of 100 Romano-Egyptians not 9 survived. Looking at these two curves we realize at a glance either the great physical progress of man, which enables him far more effectually to withstand a hostile environment, or the great social and sanitary progress he has made which enables him to modify the environment. In either case we can definitely assert that 2,000 years has made him a much 'fitter' being. In this comparison it must be remembered that we are not placing a civilized race against a barbaric tribe, but comparing a modern civilization with one of the highest types of ancient civilization."

Macdonell was able to continue this investigation on much more extensive material extracted from the *Corpus*

Inscriptionum Latinarum of the Berlin Academy, which gives records as to age of death for many thousand Roman citizens dying, for the most part, within the first three or four centuries of the Christian era. His material may, therefore, be taken to represent the conditions a few centuries later than those of Pearson's Romano-Egyptian population. Macdonell was able to calculate

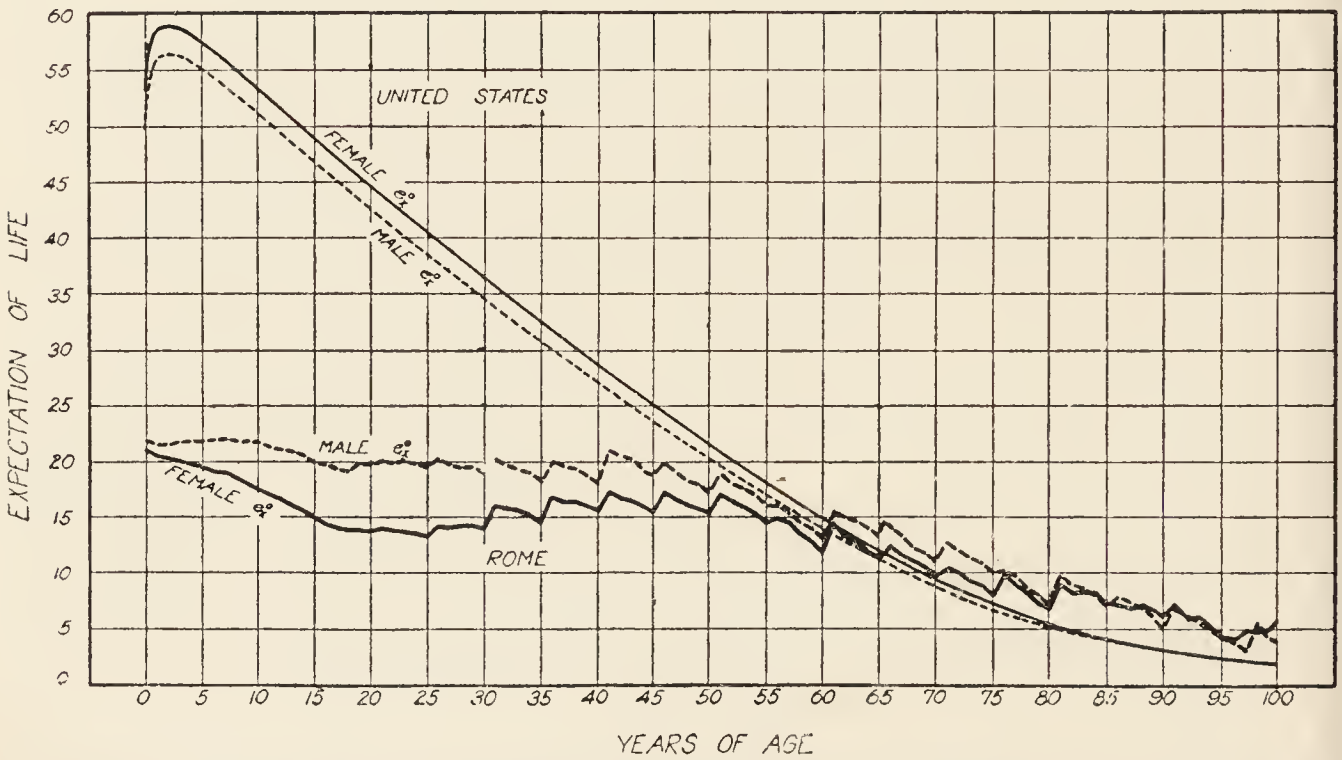


FIG. 22.—Comparing the expectation of life of Ancient Romans with that of present day Americans. Plotted from Macdonell's and Glover's data.

three tables of expectation of life—the first for Roman citizens living in the city of Rome itself; second for those living in the provinces of Hispania and Lusitania; and third, for those living in Africa. The results are plotted against the United States 1910 data, as before, in Figures 22, 23, and 24.

Figure 22 relates to inhabitants of the city of Rome itself. The deaths from which the expectations are calculated run into the thousands, and fortunately one is able to separate males and females. As in Pearson's case, which we have just examined, modern American

data are entered for comparison. It will be noted at once that just as in the Romano-Egyptian population the expectation of life of inhabitants of ancient Rome was, in the early years of life, apparently immensely inferior to that of the modern population. From about the age of 60 on, however, the expectation of life appears to have been better then than now. Curiously enough, the expectation

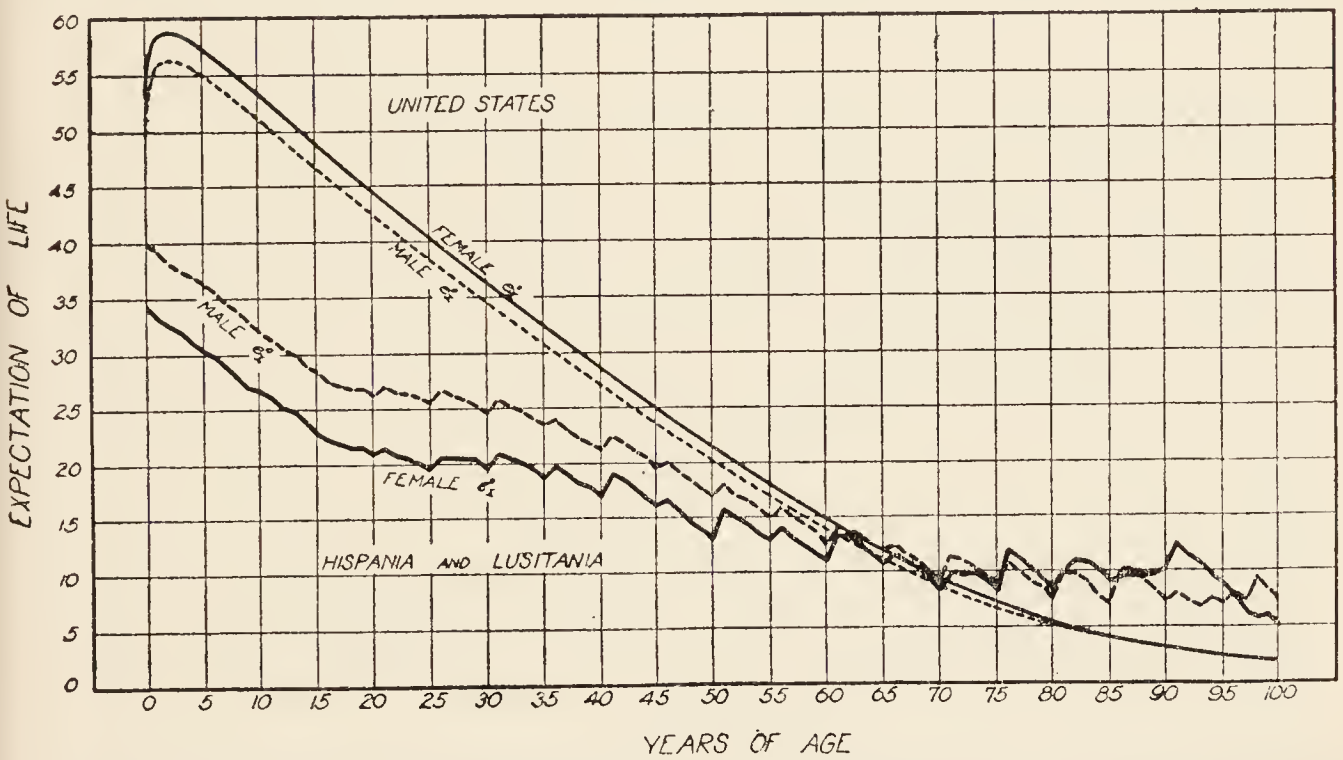


FIG. 23—Comparing the expectation of life of the population of the Roman provinces Hispania and Lusitania with that of present day Americans. Plotted from Macdonell's and Glover's data.

of life of females was poorer at practically all ages of life than that of the males which exactly reverses the modern state of affairs. Macdonell believes this difference to be real and to indicate that there were special influences adversely affecting the health of females in the Roman Empire, which no longer operate in the modern world. Up to something like age 25 the expectation of life of dwellers in the city of Rome was extremely bad, worse than in the Romano-Egyptian population which Pearson studied, or in the populations of other parts of the Roman Empire as we shall see in the following diagram. Macdonell thinks

that this difference is real and due to circumstances peculiar to Rome.

The general features of the diagram for the population of Hispania and Lusitania (Figure 23) are similar to those that we have seen, with the difference that the expectation of life up to age 20 or 25 is not as bad as in the city of Rome itself. Again the females show a lower expectation practically throughout life than do the males.

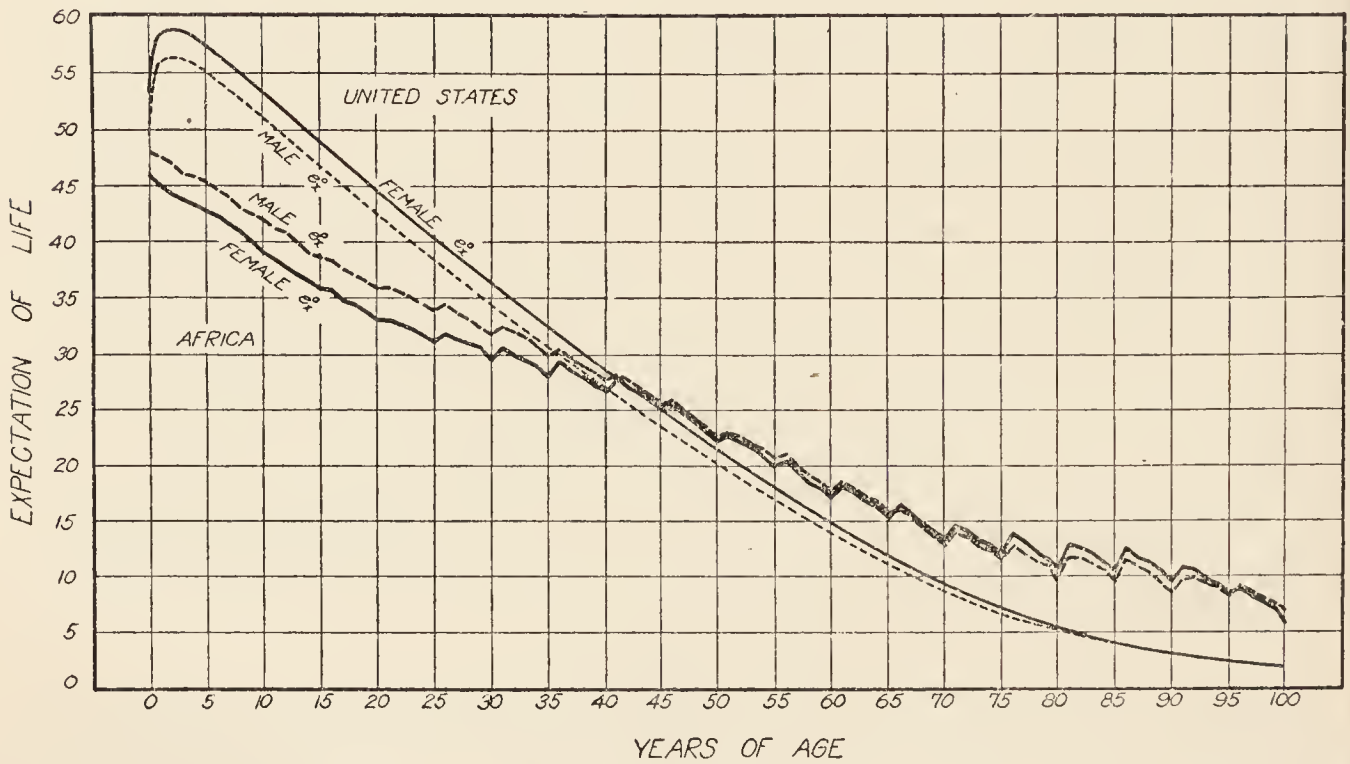


Fig. 24—Comparing the expectation of life of the population of the Roman provinces in Africa with that of present day Americans. Plotted from Macdonell's and Glover's data.

The lines cross the modern American lines at about age 60 and from that point on these colonial Romans apparently had a better expectation of life than the modern American has.

The Romano-African population diagram appears to start at nearly the same point at birth as does the modern American, and in general the differences up to age 35 are not substantially more marked from modern conditions than they are in the seventeenth century Breslau table. The striking thing, however, is that at about age

40 the lines cross, and from then on the expectation of life was definitely superior in the early years of the Christian era to what it is now.

It should be said that the curious zigzagging of the lines in all of these Roman tables of Macdonell is due to the tendency, which ancient Romans apparently had in common with present day American negroes, towards heavy grouping on the even multiples of 5 in the statement of their ages.

Summarizing the whole matter we see that during a period of approximately 2,000 years man's expectation of life at birth and subsequent early ages has apparently been steadily improving, while at the same time his expectation of life at advanced ages has been steadily worsening. The former phenomenon may probably be attributed essentially to ever increasing knowledge of how best to cope with the lethal forces of nature.* Progressively better sanitation, in the broadest sense, down through the centuries has saved for a time the lives of ever more and more babies and young people who formerly could not withstand the unfavorable conditions they met, and died in consequence rather promptly. But just because this process tends to preserve the weaklings, who were speedily eliminated under the rigorous action of unmitigated nat-

---

* No absolute reliance can, of course, be put upon Macdonell's or Pearson's curves. Besides laboring under the serious actuarial difficulty of being expectations calculated from a knowledge of deaths alone, the randomness of the sampling, even on that basis, is extremely doubtful. The only real evidence that these Roman curves represent a rough picture of the truth as to expectation of life in those days, arises from the consideration that they show a difference from present-day expectations which is of the same *kind* as that which is found between populations of one and two centuries ago and the present, and of a greater *amount*, as would be expected from the longer time interval, and from what we know has occurred in the material development of civilization in the meantime.

ural selection, there appear now in the higher age groups of the population many weaker individuals than formerly ever got there. Consequently the average expectation of life at ages beyond say 60 to 70 is not nearly so good now as it was under the more rigorous régime of ancient times. Then, any individual who attained age 70 was the surviving resultant of a bitterly destructive process of selection. To run successfully the gauntlet of early and middle life, he necessarily had to have an extraordinarily vigorous and resistant constitution. Having come through successfully to 70 years of age it is no matter of wonder that his prospects were for a longer old age than his descendants of the same age to-day can look forward to. Biologically, these expectation of life curves give us the first introduction to a principle which we shall find as we go on to be of the very foremost importance in fixing the span of human longevity, namely that *inherited constitution fundamentally and primarily determines how long an individual will live.*

ANALYSIS OF THE LIFE TABLE

I shall not develop this point further now, but instead will turn back to consider briefly certain features of the d_x line of a life table. Figure 18 shows that this line, which gives the number of deaths occurring at each age, has the form of a very much stretched letter S resting on its back. Some years ago, Pearson undertook the analysis of this complex curve, and drew certain interesting conclusions as to the fundamental biological causes lying behind its curious sinuosity. His results are shown in Figure 25.

He regarded the d_x line of the life table as a compound curve, and by suitable mathematical analysis broke it up

into five component frequency curves. The data which he used were furnished by the d_x line of Ogle's life table, based on the experience of 1871 to 1880 in England. This line gives the deaths per annum of one thousand persons born in the same year. The first component which he separated was the old age mortality. This is shown by the dotted curve having its modal point between 70 and 75 years, at the point lettered O_1 on the base of the diagram.

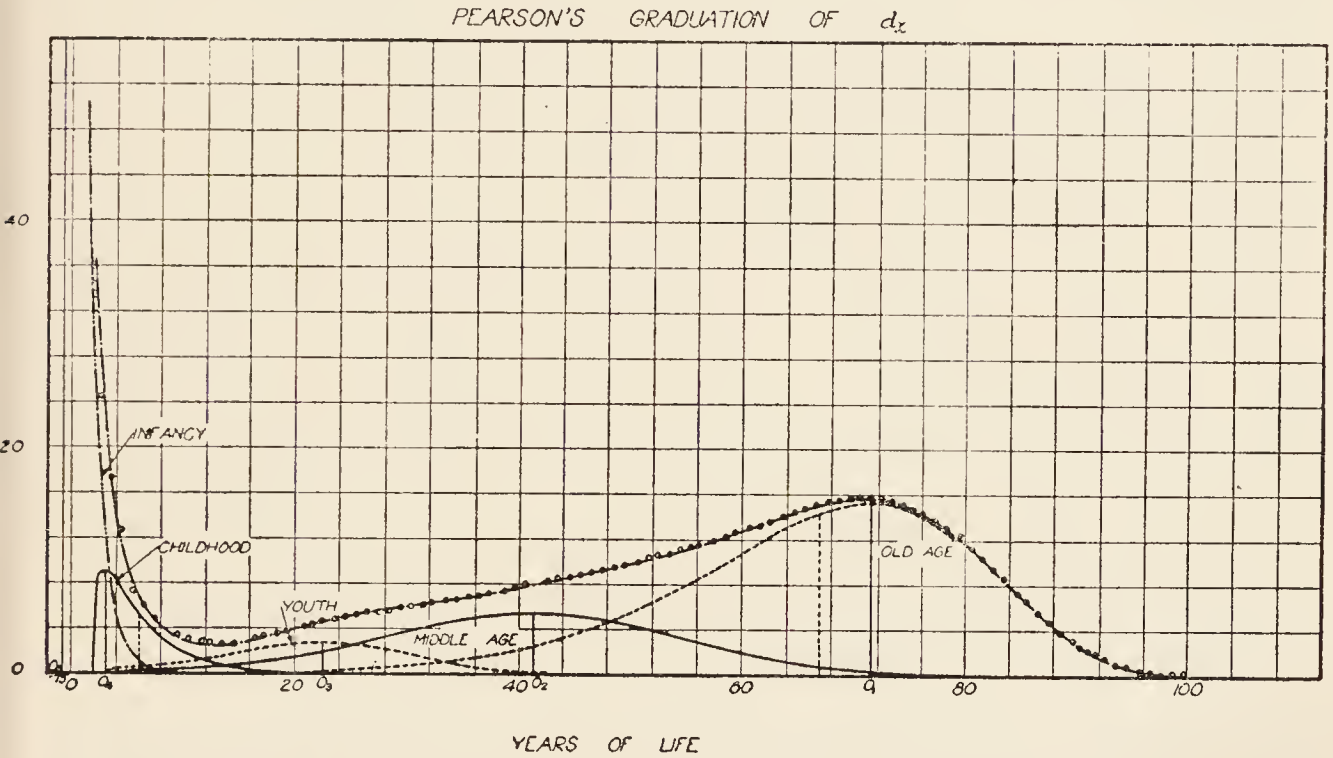


FIG. 25.—Showing Pearson's results in fitting the d_x line of the life table with 5 skew frequency curves. Plotted from the data of Pearson's original memoir on "Skew Variation" in Phil. Trans. Roy. Soc.

This component, according to Pearson's graduation, accounted for 484.1 deaths out of the total of 1,000, or nearly one-half of the whole. Its range extends from under 20 years of age to the upper limit of life, at approximately 106 years. The second component includes the deaths of middle life. This is the smooth curve having its modal point between 40 and 45 years at the point on the base marked O_2. Its range extends from about 5 years of age to about 65. It accounts for 175.2 deaths out of the total of 1,000. It is a long, much spread out

curve, exhibiting great variability. The third component is made up by the deaths of youth. This accounts for 50.8 deaths out of the total of a thousand, and its range extends from about the time of birth to nearly 45 years. Its mid-point is between 20 and 25 years, and it exhibits less variability than either the middle life or the old age curves. The fourth component, the modal point of which is at the point on the base of the diagram marked O_4 covers the childhood mortality. It accounts for 46.4 deaths out of the total of 1,000. Its range and variability are obviously less than those of any of the other three components so far considered. The last, excessively skew component, is that which describes the mortality of infancy. It is given by a J shaped curve accounting for 245.7 deaths after birth, and an antenatal mortality of 605. In order to get any fit at all for this portion of the mortality curve it is necessary to assume that the deaths *in utero* and those of the first months after birth are a homogeneous connected group.

Summing all these components together it is seen that the resulting smooth curve very closely fits the series of small circles which are the original observations. From the standpoint merely of curve fitting no better result than this could be hoped for. But about its biological significance the case is not quite so clear, as we shall presently see.

Pearson himself thinks of these five components of the mortality curve as typifying five Deaths, shooting with different weapons, at different speeds and with differing degrees of precision at the procession of human beings crossing the Bridge of Life. The first Death is, according to Pearson, a marksman of deadly aim, concentrated fire, and unremitting destructiveness. He kills

before birth as well as after and may be conceived as beating down young lives with the bones of their ancestors. The second marksman who aims at childhood has an extremely concentrated fire, which may be typified by the machine gun. Only because of the concentration of this fire are we able to pass through it without appalling loss. The third marksman Death, who shoots at youth has not a very deadly or accurate weapon, perhaps a bow and arrow. The fire of the fourth marksman is slow, scattered and not very destructive, such as might result from an old fashioned blunderbuss. The last Death plies a rifle. None escapes his shots. He aims at old age but sometimes hits youth. His unremitting activity makes his toll large.

We may let Pearson sum the whole matter up in his own words: "Our investigations on the mortality statistics have thus led us to some very definite conclusions with regard to the chances of death. Instead of seven we have five ages of man, corresponding to the periods of infancy, of childhood, of youth, of maturity or middle age, and of senility or old age. In the case of each of these periods we see a perfectly regular chance distribution, centering at a given age, and tailing off on either side according to a perfectly clear mathematical law. . .

"Artistically, we no longer think of Death as striking chaotically; we regard his aim as perfectly regular in the mass, if unpredictable in the individual instance. It is no longer the Dance of Death which pictures for us Death carrying off indiscriminately the old and young, the rich and the poor, the toiler and the idler, the babe and its grandsire. We see something quite different, the cohort of a thousand tiny mites starting across the Bridge of Life, and growing in stature as they advance,

till at the far end of the bridge we see only the gray-beard and the 'lean and slippered pantaloon.' As they pass along the causeway the throng is more and more thinned; five Deaths are posted at different stages of the route longside the bridge, and with different skewness of aim and different weapons of precision they fire at the human target till none remains to reach the end of the causeway—the limit of life.''

This whole, somewhat fanciful, conception of Pearson's needs a little critical examination. What actually he has done is to get a good empirical fit of the d_x line by the use of equations involving all told some 17 constants. Because the combined curve fits well, *and fundamentally for no other reason,* he implicitly concludes that the fact that the fit is got by the use of five components means biologically that the d_x line is a compound curve, and indicates a five-fold biological heterogeneity in the material. But it is a very hazardous proceeding to draw biological conclusions of this type from the mere fact that a theoretical mathematical function or functions fits well a series of observational data. I fully discussed this point several years ago and pointed out:

''The kind of evidence under discussion can at best have but inferential significance; it can never be of demonstrative worth. It is based on a process of reasoning which assumes a fundamental or necessary relationship to exist between two sets of phenomena because the same curve describes the quantitative relations of both sets. A little consideration indicates that this method of reasoning certainly cannot be of general application, even though we assume it to be correct in particular cases. The difficulty arises from the fact that the mathematical functions commonly used with adequate results in physi-

cal, chemical, biological, and mathematical investigations are comparatively few in number. The literature of science shows nothing clearer than that the same type of curve frequently serves to describe with complete accuracy the quantitative relations of widely different natural phenomena. As a consequence, any proposition to conclude that two sets of phenomena are causally or in any other way fundamentally related solely because they are described by the same type of curve is of a very doubtful validity.''

Henderson has put Pearson's five components together in a single equation, as follows:

$$l_x \mu_x = 15.2\left(1-\frac{x-71.5}{35}\right)^{7.7525} e^{0.2215\,(x-71.5)} + 5.4\,e^{-[.05524\,(x-41.5)]^2} + 2.6\,e^{-[.09092\,(x-22.5)]^2} + 8.5\left(x-2\right)^{.3271} e^{-.3271\,(x-3)} + 415.6\left(x+.75\right)^{-.5} e^{-.75\,(x+.75)}$$

Henderson says regarding this method of Pearson's for analyzing the life table: ''. . . it is difficult to lay a firm foundation for it, because *no analysis of the deaths into natural divisions by causes or otherwise has yet been made* such that the totals in the various groups would conform to those frequency curves.'' The italics in this quotation are the present writer's for the purpose of emphasizing the crucial point of the whole matter.

Now it is altogether probable that one could get just as good a fit to the observed d_x line as is obtained by Pearson's five components by using a 17 constant equation of the type

$$y = a + bx + cx^2 + dx^3 + ex^4 + fx^5 + gx^6 + \ldots\ldots\ldots + nx^{16}$$

and in that event one would be quite as fully justified (or really unjustified) in concluding that the d_x line was a homogeneous curve as Pearson is in concluding from his five-component fit that it is compound. Indeed Wittstein's formula involving but four constants

$$q_x = a^{-(M-x)^n} + \frac{1}{m} a^{-(mx)^n}$$

gives a substantially good fit over the whole range of life. It is, of course, apparent that the formula as here given is in terms of another function, q_x, of the life table, rather than the d_x which we have hitherto been discussing. But no difference is in fact involved. q_x values may be immediately converted into d_x values by a simple arithmetical transformation.

But in neither Pearson's, Wittstein's, nor any other case is the curve-fitting evidence, by and of itself, in any sense a demonstration of the biological homogeneity or heterogeneity of the material. Of far greater importance, and indeed conclusive significance, is the fact, to be brought out in a later chapter, that in material *experimentally known to be biologically homogeneous,* a population made up of full brothers and sisters out of a brother x sister mating and kept throughout life in a uniform environment identical for all individuals, *one gets a d_x line in all its essential features,* save for the absence of excessive infant mortality arising from perfectly clear biological causes, *identical with the human d_x line.* It has long been apparent to the thoughtful biologist that there was not the slightest biological reason to suppose that the peculiar sinuosity of the human d_x line owed its origin to any fundamental heterogeneity in the material, or differentiation in respect of the forces of mortality.

Now we have experimental proof, to be discussed in a later chapter, that with complete homogeneity of the material, both genetic and environmental, one gets just the same kind of d_x line as in normal human material. We must then, I think, come to the conclusion that brilliant and picturesque as is Pearson's conception of the five Deaths, actually there is no slightest reason to suppose that it represents any *biological* reality, save in the one respect that his curve fitting demonstrates, as any other equally successful would, that deaths do not occur chaotically in respect of age, but instead in a regular manner capable of representation by a mathematical function of age.

An interesting and suggestive analysis of the d_x line, resting upon a sounder biological basis than Pearson's, has lately been given by Arne Fisher. He breaks the curve up into 8 or 9 components, based upon the comparatively stable values of the death ratios for different groups of diseases characteristic of different ages. The resulting total curve fits the facts from age 10 on, very well, and makes possible the calculation of a complete life table from a knowledge of deaths only.

CHAPTER IV

THE CAUSES OF DEATH

It has been suggested in earlier chapters that natural death of the metazoan body may come about fundamentally because of the differentiation and consequent mutual dependence of structure and function of that body. It is a complex aggregate of cells and tissues, all mutually dependent upon each other and in a delicate state of adjustment and balance. If one organ for any accidental reason, whether internal or external, fails to function normally it upsets this delicate balance, and if normal functioning of the part is not promptly restored, death of the whole organism eventually results. Furthermore, it is apparent that death does not strike in a haphazard or random manner, but instead in a most orderly way. There are certain periods of life—notably youth—where only an insignificant fraction of those exposed to risk ever die. At other ages, as, for example, extreme old age and early infancy, death strikes with appalling precision and frequency. Further we recall with Seneca that *nascimus uno modo multis morimur.* Truly there are many ways of dying. The fact is obvious enough. But what is the biological meaning of this multiplicity of pathways to the river Styx? There is but one pathway into the world. Why so many to go out? To the consideration of some phases of this problem attention is directed in this chapter.

By international agreement among statisticians the causes of human mortality are, for statistical purposes,

rather rigidly defined and separated into something over 180 distinct units. It should be clearly understood that this convention is distinctly and essentially statistical in its nature. In recording the statistics of death the registrar is confronted with the absolute necessity of putting every demise into some category or other in respect of its causation. However complex biologically may have been the train of events leading up to a particular end, the statistician must record the terminal "cause of death" as some particular thing. The International Classification of the Causes of Death is a code which is the result of many years' experience and thought. Great as are its defects in certain particulars, it nevertheless has certain marked advantages, the most conspicuous of which is that by its use the vital statistics of different countries of the world are put upon a uniform basis.

The several separate causes of death are grouped in the International Classification into fourteen general classes. These are:

I. General diseases.
II. Diseases of the nervous system and of the organs of special sense.
III. Diseases of the circulatory system.
IV. Diseases of the respiratory system.
V. Diseases of the digestive system.
VI. Non-venereal diseases of the genito-urinary system and annexa.
VII. The puerperal state.
VIII. Diseases of the skin and of the cellular tissue.
IX. Diseases of the bones and organs of locomotion.
X. Malformation.
XI. Early infancy.
XII. Old age.
XIII. External causes.
XIV. Ill-defined diseases.

Perhaps the most outstanding feature which strikes one about the International List is that it is not primarily

a biological classification. Its first group, for example, called "General Diseases," which caused in 1916 in the Registration Area of the United States approximately one-fourth of all the deaths, is a most curious biological and clinical mélange. It includes such diverse entities as measles and malaria, tetanus and tuberculosis, cancer and gonococcus infection, alcoholism and goiter, and many other unlike causes of death. For the purposes of the statistical registrar it perhaps has useful points to make this "General Diseases" grouping, but it clearly corresponds to nothing natural in the biological world. Again in such parts of the scheme as do have some biological foundation the basis is different in different rubrics. Some have an organological basis, while others have a causational.

For purposes of biological analysis, I developed some time ago an entirely different classification of the causes of death, on what appears to be a reasonably consistent basis.* The underlying idea of this new classification was to group all causes of death under the heads of the several organ systems of the body, the functional breakdown of which is the immediate or predominant cause of the cessation of life. All except a few of the statistically recognized causes of death in the International Classification can be assigned places in such a biologically

* It should be clearly understood that I am not advocating a new classification of the causes of death for statistical use. I should oppose vigorously any attempt to substitute a new classification (mine or any other) for the International List now in use. Uniformity in statistical classification is essential to usable, practical vital statistics. Such uniformity has now become well established through the International Classification. It would be most undesirable to make any radical changes in the Classification now. I have made a rearrangement of the causes of death, for the purposes of a specific biological problem, and no other. I am not "proposing a new classification of vital statistics" for official or any other use except the one to which it is here put.

grouped list. It has a sound logical foundation in the fact that, biologically considered, death results because some organ system, or group of organ systems, fails to continue its functions.

The headings finally decided upon in the new classification were as follows:

I. Circulatory system, blood and blood-forming organs.
II. Respiratory system.
III. Primary and secondary sex organs.
IV. Kidneys and related excretory organs.
V. Skeletal and muscular systems.
VI. Alimentary tract and associated organs concerned in metabolism.
VII. Nervous system and sense organs.
VIII. Skin.
IX. Endocrinal system.
X. All other causes of death.

The underlying idea of this rearrangement of the causes of death is to put all those lethal entities together which bring about death because of the functional organic breakdown of the same general organ system. The cause of this functional breakdown may be anything whatever in the range of pathology. It may be due to bacterial infection; it may be due to trophic disturbances; it may be due to mechanical disturbances which prevent the continuation of normal function; or to any cause whatsoever. In other words the basis of the classification is *not* that of pathological causation, but it is rather that of organological breakdown. We are now looking at the question of death from the standpoint of the biologist, who concerns himself not with what causes a cessation of function, but rather with what part of the organism ceases to function, and therefore causes death.

In a series of papers already published I have given a detailed account of this classification, and the reasoning on which particular causes of death are placed in it where

they are. Space is lacking here to go into the details, and I must consequently ask the reader either to take it on faith for the time being that the classification is at least a fairly reasonable one, or to take the trouble to go over it in detail in the original publication.*

GENERAL RESULTS OF BIOLOGICALLY CLASSIFIED DEATH RATES

Here I should like to present first some general statistical results of this classification. The data which we shall first discuss are in the form of death rates, from various causes, per hundred thousand living at all ages, arranged by organ systems primarily concerned in death from specified diseases. The statistics came from three widely separated localities and times, *viz.*, (a) from the Registration Area of the United States; (b) from England and Wales; and (c) from the City of São Paulo, Brazil.

The summarized results are shown in Table 7, and in graphic form in Figure 26.

The rates are arranged in descending order of magnitude for the United States Registration Area, with the exception of those of group X, all other causes of death. We note in passing that this biologically unclassifiable group includes roughly 10 to 15 per cent of the total mortality. It may be well to digress a moment to consider why these deaths cannot be put into our general scheme. Table 8 exhibits the rates included in class X.

This residue comprises in general three categories (*a*) accidental and homicidal deaths; (*b*) senility; and

* *Cf.* particularly Pearl, R. "On the embryological basis of human mortality." (Proc. Natl. Acad. Sci. Vol. 5, pp. 593-598, 1919) and "Certain evolutionary aspects of human mortality rates." (Amer. Natl. Vol. LIV. pp. 5-44, 1920). The following section as well as Chapter V are largely based upon the second of the two papers.

(*c*) deaths from a variety of causes which are statistically lumped together and cannot be disentangled. Accidental and homicidal deaths find no place in a biologi-

TABLE 7

Showing the Relative Importance of Different Organ Systems in Human Mortality

Group No.	Organ System	Death Rates per 100,000			
		Registration Area, U. S. A.		England and Wales 1914	São Paulo 1917
		1906–10	1901–05		
II	Respiratory system	395.7	460.5	420.2	417.5
VI	Alimentary tract and associated organs	334.9	340.4	274.1	613.8
I	Circulatory system, blood	209.8	196.8	208.6	254.8
VII	Nervous system and sense organs	175.6	192.9	151.9	124.3
IV	Kidneys and related excretory organs	107.2	107.4	19.4	83.4
III	Primary and secondary sex organs	88.1	77.4	95.4	103.2
V	Skeletal and muscular system	12.6	13.7	18.2	6.8
VIII	Skin	10.1	13.3	12.0	7.9
IX	Endocrinal system	1.5	1.2	1.9	1.1
	Total death rate classifiable on a biological basis	1,335.5	1,403.6	1,201.7	1,612.8
X	All other causes of death	171.3	211.8	141.4	109.8

cal classification of mortality. A man organically sound in every respect may be instantly killed by being struck by a railroad train or an automobile. The best possible case that could be made out for a biological factor in such deaths would be that contributory carelessness or negligence, which is a factor in some portion of accidental deaths, bespeaks a small but definite organic mental inferiority or weakness, and that, therefore, accidental deaths should be charged against the nervous system. This, however, is obviously not sound. For, in the first place, in many accidents there is no factor of contributory

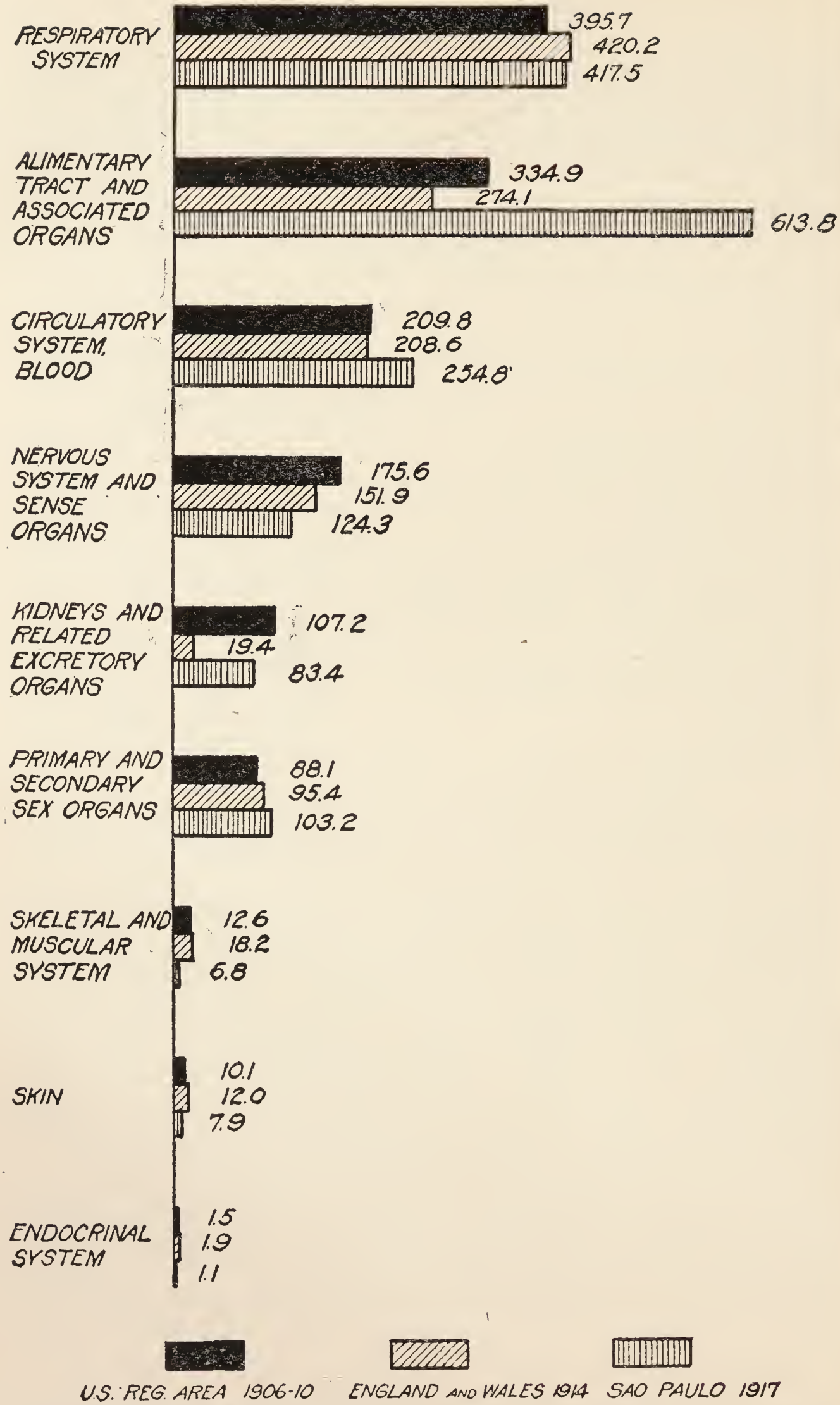


FIG. 26.—Showing the relative importance of the different organ systems in human mortality.

negligence in fact, and, in the second place, in those cases where such negligence can fairly be alleged its degree or significance is undeterminable and in many cases surely slight.

Senility as a cause of death is not further classifiable

TABLE 8

All Other Causes

No.	"Cause of Death" as per International Classification	Registration Area, U. S. A.		England and Wales 1914	São Paulo 1917
		1906–10	1901–05		
	All external causes (except suicide)	91.9	87.8	26.1	36.4
187, 188 & 189	Ill-defined diseases	29.4	47.8	7.3	36.3
154	Senility	29.0	41.0	81.5	11.1
45	Cancer of other organs or of organs not specified	12.9	16.1	16.6	17.9
152*	Other causes peculiar to early infancy	3.4	2.6	5.1	3.3
34	Tuberculosis of other organs	2.1	2.0	1.6	0.2
46	Other tumors (female genital organs excepted)	1.0	1.5	0.5	0.9
55	Other general diseases	1.0	0.5	1.5	3.5
153	Lack of care	0.3	12.3	0.6	0
19	Other epidemic diseases	0.3	0.2	0.6	0.2
	Totals	171.3	211.8	141.4	109.8

* In part.

on an organological basis. A death really due to old age, in the sense of Metchnikoff, represents, from the point of view of the present discussion, a breaking down or wearing out of all the organ systems of the body contemporaneously. In a strict sense this probably never, or at best extremely rarely, happens. But physicians and registrars of mortality still return a certain number of deaths as due to "senility." Under the circumstances

it is not possible to go behind such returns biologically.

The second line of Table 8, "Ill-defined diseases," furnishes a striking commentary on the relative efficiency of the medical profession in the United States and England in respect of the reporting of the causes of death. Only about one-fourth as many deaths appear in the English vital statistics as due to ill-defined and unknown causes as in the United States figures.

Returning now to the consideration of the general results set forth in Table 7 and Figure 26, a number of interesting points about human mortality are apparent. In the United States, during the decade covered, more deaths resulted from the breakdown of the respiratory system than from the failure of any other organ system of the body. The same thing is true of England and Wales. In São Paulo the alimentary tract takes first position, with the respiratory system a rather close second. The tremendous death rate in São Paulo chargeable to the alimentary tract is chiefly due to the relatively enormous number of deaths of infants under two from diarrhœa and enteritis. Nothing approaching such a rate for this category as São Paulo shows is known in this country or England.

In all three localities studied the respiratory and the alimentary tract together account for rather more than half of all the deaths biologically classifiable. These are the two organ systems which, while physically internal, come in contact directly at their surfaces with environmental entities (water, food, air) with all their bacterial contamination. The only other organ system directly exposed to the environment is the skin. The alimentary canal and the lungs are, of course, in effect invaginated *surfaces* of the body. The mucous membranes which line them are far less resistant to environmental stresses,

both physical and chemical, than is the skin with its protecting layers of stratified and cornified epithelium.

The organs concerned with the blood and its circulation—the heart, arteries and veins, etc.—stand third in importance in the mortality list. Biologically the blood, through its immunological mechanism, constitutes the second line of defense which the body has against noxious invaders. The first line is the resistance of the outer cells of the skin and the lining epithelium of alimentary tract, lungs, and sexual and excretory organs. When invading organisms pass or break down these first two lines of defense, the battle is then with the home guard, the cells of the organ system itself, which, like the industrial workers of a commonwealth, keep the body going as a whole functioning mechanism. Naturally it would be expected that the casualties would be far heavier in the first two defense lines (respiratory and alimentary systems and the blood and circulation) than in the home guard. Death rates, when biologically classified, bear out this expectation.

In the United States the kidneys and related excretory organs are responsible for more deaths than the sex organs. This relation is reversed in England and Wales, and in São Paulo. This difference is mainly due in both countries to premature birth. The higher premature birth rate for these two localities as compared with the United States might conceivably be explained in any one of several ways. It might mean better obstetrics here than in the other localities, or it might mean that the women of this country, as a class, are somewhat superior physiologically in the matter of reproduction, when they do reproduce, or it might be in some manner connected with differences in birth rates.

The last three organ systems, skeletal and muscular system, skin and endocrinal organs, are responsible for so few deaths relatively as not to be of serious moment.

There is one general consequence of these results upon which I should like to dwell a moment longer. In a broad sense the efforts of public health and hygiene have been directed against the affections comprised in the first two items in the chart, those of the respiratory system and the alimentary tract. The figures for the two five-year periods in the United States, 1901-05 and 1906-10, indicate roughly the rate of progress such measures are making, looking at the matter from a broad biological standpoint. In reference to the respiratory system there was a decline of fourteen per cent. in the death rate between the two periods. This is substantial. It is practically all accounted for in phthisis, lobar pneumonia and bronchitis. For the alimentary tract the case was not so good—indeed far worse.

Between the two periods the death rate from this cause group fell only 1.8 per cent. All the gain made in typhoid fever was a great deal more than offset by diarrhœa and enteritis (under two), congenital debility and cancer. Child welfare, both prenatal and postnatal, seems by long odds the most hopeful direction in which public health activities can expect, at the present time, substantially to reduce the general death rate. This is a matter fundamentally of education.

SPECIFIC DEATH RATES BIOLOGICALLY CLASSIFIED

Up to this point in our discussions we have been dealing with crude death rates, uncorrected for the age and sex distributions of the populations concerned. It is, of course, a well known fact that differences in age and

sex constitution of populations may make considerable differences in crude death rates, in cases where no real differences in the true force of mortality exist. What is essential for the further prosecution of the analysis of the causes of death is to get *specific* death rates for the several causes. By an age and sex specific death rate is meant the rate got by dividing the number of persons, of *particular specified age and sex,* dying from a particular cause, by the total number of persons living in the same population *of the same age and sex.* In other words, we need to get as the divisor of the rate fraction the number of persons who can be regarded as truly exposed to risk. This exposed-to-risk portion of the population is never correctly stated in a crude death rate. For example, a person now 75 years old cannot be regarded as exposed to risk of death at age 45. He was once exposed to that risk but passed it safely. Yet in a crude death rate he is counted with those of age 45.

Age and sex specific death rates have hitherto been available for the American people, in any general or comprehensive form, only from the extensive memoir by Dublin, Kopf and Van Buren, based upon the mortality experience of the Metropolitan Life Insurance Company with its industrial policy holders. In a broad way, it may be said that the data on which the following discussion is based, derived from the general population of the Registration Area, are essentially in accord with those of Dublin on a more restricted group. Owing to limitations of space, it is not possible to present all the detailed rates here.

With the aid of Dr. William H. Davis, director of vital statistics in the Census Bureau, who very kindly provided me with the necessary unpublished data, it has

been possible to calculate the specific death rates for each of the 189 causes of death of the International List, for each sex separately, and for each age in 5 year groups, for the United States Registration Area, exclusive of North Carolina, in 1910. These results have been put together in the biological scheme of classification and may be presented briefly in the form of diagrams.

The summary table from which these curves are plotted is given as Table 9.

Let us first consider deaths from all causes taken together, in order to recall to mind the general form of a death rate curve. It will be noted, at once, that the rates are plotted along the vertical axis on what strikes one at first as a peculiar scale. The scale is logarithmic. The horizontal lines are spaced in proportion to the logarithms of the numbers at their left, instead of in proportion to the numbers themselves. The advantages of this method of plotting in the present case are two-fold. First, it is possible to get a much wider range of values on the diagram; and second the logarithmic scale permits direct and accurate estimation of the rate of change of a variable. A straight line forming an angle with the horizontal on a logarithmic scale means that the variable is increasing or decreasing, as the case may be, *at a constant rate of change.*

Figure 27 gives the specific death rates for the combined total of all causes. The curve in general has the form of a V, with one limb much extended and pulled over to the right. Examining it more in detail, we note that in the first year of life, the specific death rate, or, as we may roughly call it, the force of mortality, bears heavier on female infants than on the males. Out of a thousand exposed to risk, 124 male babies die in that year,

TABLE 9

Showing the Specific Death Rates, per 1000 Living of the same Age and Sex, for each Biological Group of Causes, in the U. S. Registration Area, exclusive of North Carolina, in 1910

Ages	Group I		Group II		Group III		Group IV		Group V		Group VI		Group VII		Group VIII		Group IX		Group X		All Causes	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
Under 1	6.87	5.13	30.15	24.68	1.74	43.16	0.93	0.63	0.40	0.34	66.32	54.25	5.46	4.58	1.01	0.97	0.01	0.005	11.50	9.69	124.38	143.43
1–4	1.00	1.00	6.89	6.53	.03	.04	.18	.18	.14	.12	4.04	3.56	1.43	1.25	.04	.04	.0005	.0009	1.34	1.12	15.09	13.84
5–9	.57	.63	1.26	1.33	.006	.006	.10	.10	.11	.11	.56	.55	.45	.41	.006	.008	—	.0001	.64	.34	3.71	3.49
10–14	.37	.45	.51	.74	.004	.008	.08	.11	.12	.11	.51	.54	.30	.25	.009	.005	.002	.003	.60	.16	2.50	2.39
15–19	.38	.40	1.38	1.52	.008	.24	.12	.21	.10	.08	.79	.70	.36	.30	.02	.01	.004	.018	.97	.22	4.14	3.69
20–24	.37	.43	2.30	2.29	.03	.69	.17	.37	.07	.06	.93	.77	.48	.33	.02	.02	.003	.027	1.59	.24	5.97	5.22
25–29	.44	.52	2.68	2.59	.04	.96	.30	.50	.06	.06	.95	.81	.60	.38	.03	.02	.004	.031	1.67	.25	6.77	6.12
30–34	.67	.68	3.15	2.57	.06	1.12	.42	.62	.07	.06	1.05	.91	.87	.49	.05	.03	.007	.04	1.65	.28	8.00	6.79
35–39	.95	.92	3.59	2.46	.07	1.25	.65	.78	.10	.07	1.27	1.18	1.19	.64	.05	.03	.009	.05	1.86	.38	9.75	7.77
40–44	1.42	1.31	3.88	2.34	.08	1.31	.98	1.00	.11	.08	1.62	1.50	1.55	.85	.09	.04	.01	.07	1.87	.43	11.61	8.93
45–49	2.06	1.91	4.15	2.32	.10	1.41	1.48	1.22	.12	.10	2.26	2.12	2.14	1.27	.13	.07	.01	.07	2.09	.53	14.54	11.03
50–54	3.13	2.71	4.57	2.67	.12	1.46	2.14	1.73	.16	.14	3.21	3.00	2.81	2.03	.16	.09	.02	.07	2.19	.73	18.51	14.63
55–59	5.11	4.24	5.46	3.54	.19	1.64	3.28	2.51	.19	.21	4.50	4.46	4.17	2.91	.23	.10	.02	.10	2.52	.90	25.66	20.62
60–64	8.25	6.79	6.59	5.07	.32	1.75	4.98	3.40	.24	.22	6.26	5.81	5.98	4.53	.34	.18	.02	.08	3.10	1.45	36.07	29.36
65–69	13.47	10.71	8.12	7.75	.73	2.00	7.05	4.94	.38	.36	8.11	8.24	8.99	7.38	.55	.28	.02	.10	4.04	2.53	51.44	44.29
70–74	21.21	17.27	10.96	11.98	1.33	2.08	10.41	7.24	.48	.57	10.27	10.71	13.19	11.21	.80	.50	.02	.09	6.44	5.17	75.10	66.82
75–79	32.73	25.41	15.94	18.21	2.24	2.53	14.87	9.68	.67	.85	13.09	13.91	20.00	17.97	1.17	.73	.02	.09	11.51	11.51	112.24	100.90
80–84	46.42	39.24	24 26	28.53	3.71	2.56	19.75	12.51	.79	1.25	17.26	17.61	27.18	25.91	1.82	1.38	.01	.05	26.94	26.84	168.14	155.87
85–89	61.79	51.33	34.66	40.70	4.38	2.83	26.76	15.78	1.07	.87	20.47	21.47	33.71	32.15	2.91	1.63	—	.02	52.16	55.95	237.91	222.74
90–94	69.00	58.83	49.65	58.13	4.45	2.89	26.21	16.02	1.68	1.31	25.60	24.34	33.78	37.91	3.61	2.01	—	.18	99.05	108.12	313.02	309.73
95–99	79.21	73.26	70.01	60.90	9.19	1.77	26.17	23.39	2.83	.44	28.29	22.51	31.12	37.51	4.24	2.65	—	—	159.03	146.51	410.18	368.93
100 and over	81.08	68.83	61.78	72.87	—	6.07	38.61	10.12	—	—	15.44	18.22	38.61	38.46	—	6.07	—	—	258.69	251.01	494.21	471.66

and 143 female. This is the only year of life in which the total force of mortality is heavier among females than males. From that time on to the end of the span of life,

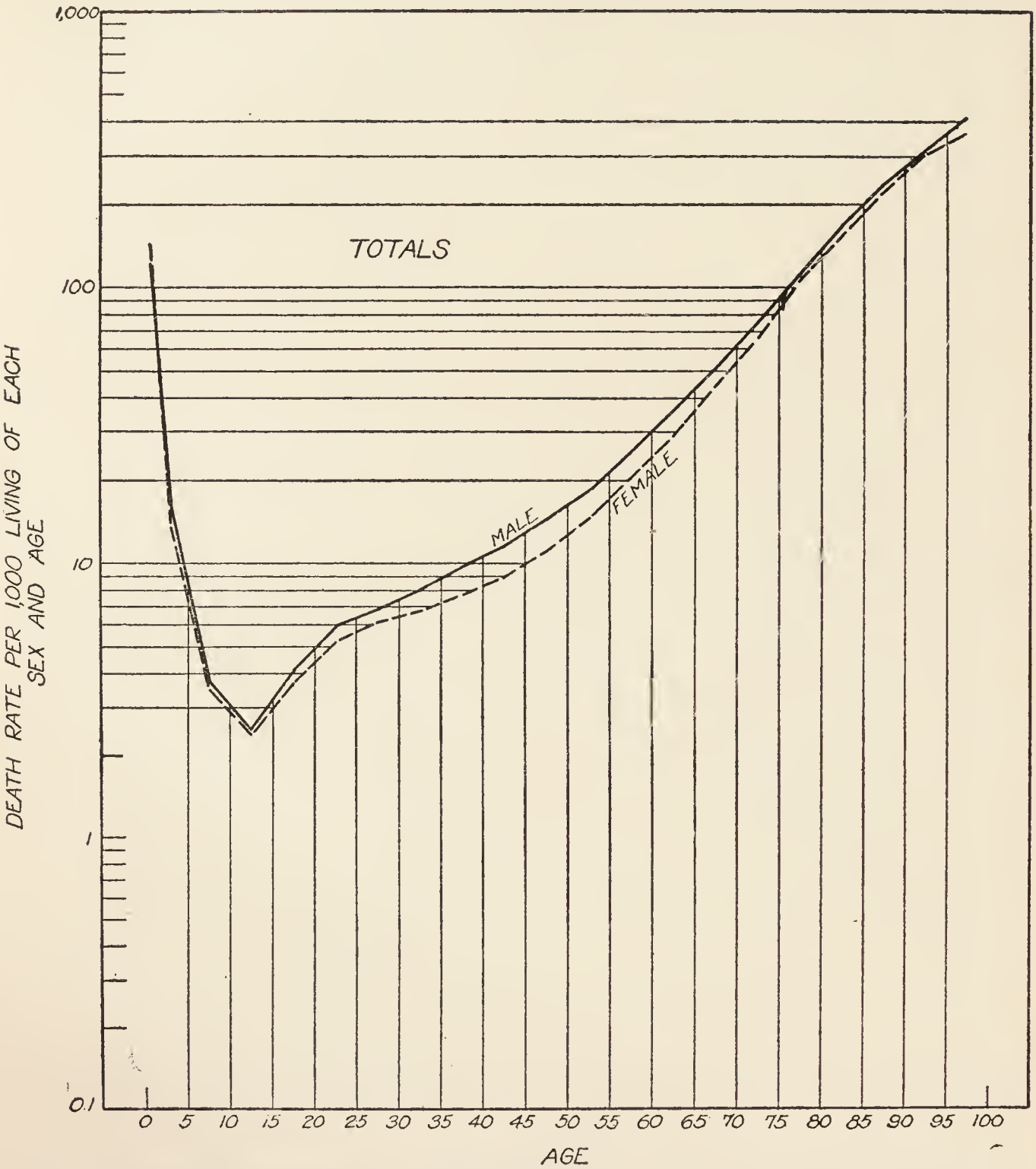


FIG. 27.—Diagram showing the specific death rate at each age for deaths from all causes taken together.

the female curve lies, by greater or less amounts, below the male curve. After the heavy mortality of early infancy, the curve drops in almost a straight line to the

age period of 10-15, where it reaches its lowest point, and only approximately 2-½ persons out of a thousand exposed to risk die. The specific mortality curve then begins to rise, and continues to do so at an approximately constant and rapid rate for ten years—that is to the age period 20-25. From then on to the age period 50-55 it rises at a slower but constant rate. This is the period of middle life, and here the female curve drops farther below the male curve than at any other place in the span of life. After the age period 50-55 with the on-coming of old age, both male and female curves begin again to rise more rapidly. They continue this rise, at a practically constant rate of increase, to the end of life, which is here taken as falling in the age period 95-100. In this last class the rate has become very high. Out of 1,000 persons living at the ages of 95 and 100, and therefore exposed to risk of death within that period, 494 males and 473 females die, taking an average for the whole five-year period. Of course, before the completion of the period, practically all of the thousand will have passed away.

The important things to note about this curve are these: First, the highest specific forces of mortality occur at the extreme ends of life, and are higher at the final end than at the beginning. In the second place, there is a sharp and steady drop, in almost a straight line, from the high specific force of mortality in infancy to the low point at about the time of puberty. From then on to the end of the span of life, the force of mortality becomes greater every year at a nearly constant rate of increase, with only such slight deviations from this constancy of rate as have already been pointed out.

Turning next to the mortality of our first biological

group—namely deaths caused by breakdown of the circulatory system, blood and blood-forming organs—we note in Figure 28 a marked difference in the form of the

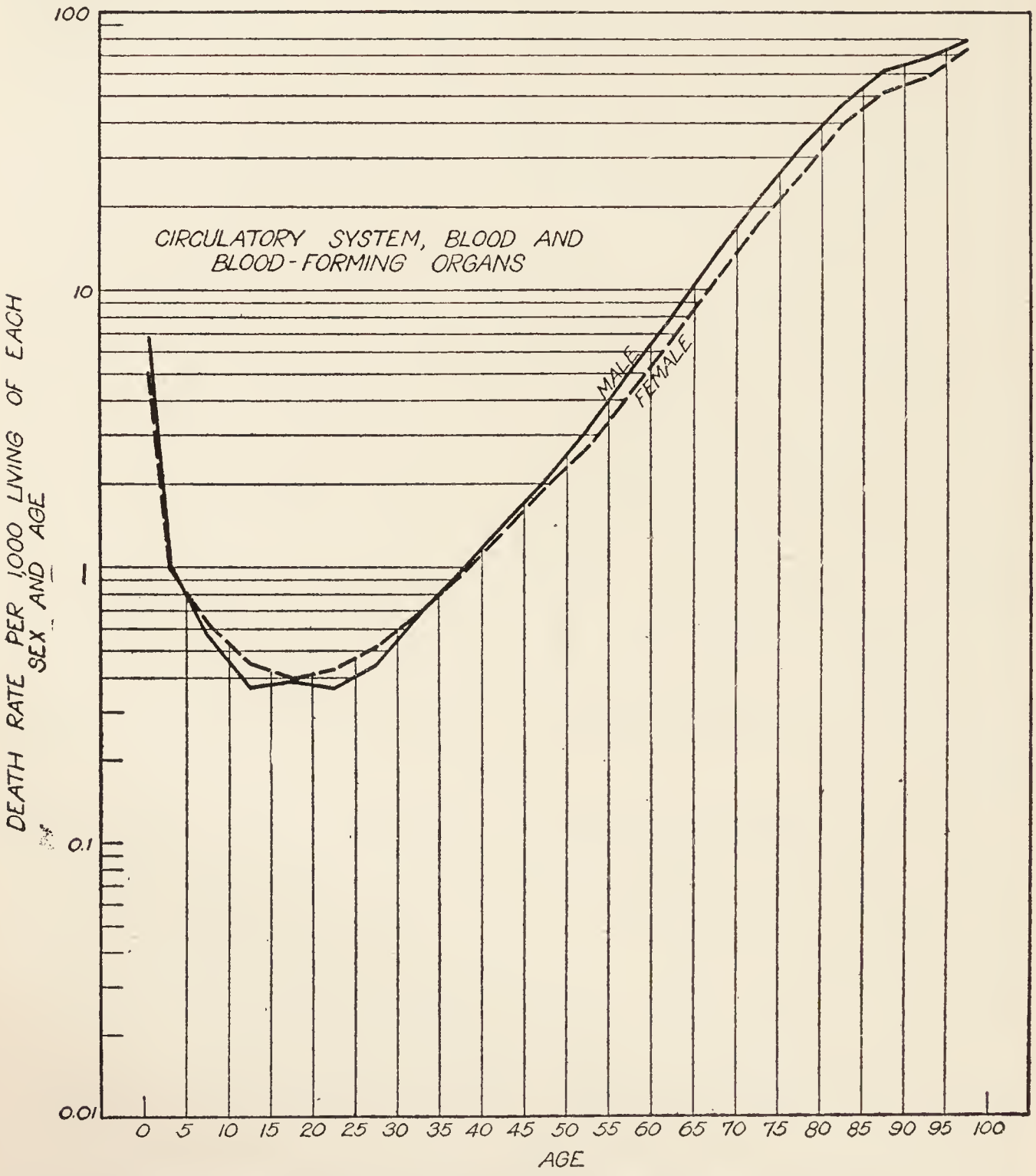


Fig. 28.—Diagram showing the specific death rate at each age from breakdown of the circulatory system, blood and blood-forming organs (Group I).

curve from what we have seen for the case of all causes of death. In the first place, the specific force of mortality of this group of causes is relatively low in infancy and

childhood. Out of a thousand infants of each sex exposed to risk, only 7 males and 5 females die from breakdown of this group of organs during the first year of life. The trough of the curve associated with the mortality of childhood and youth is very much less pointed than in the case of "all causes." It is a smoothly rounded, rather than a sharply pointed depression. It is also noteworthy that between approximately the ages of 5 and 35 the specific force of mortality from diseases of the circulatory system and related organs is higher for females than it is for males. This condition of affairs is probably connected with the graver physiological changes and readjustments called forth by puberty in the female than accompany the same vital crisis in the male. From early adult life, say age 25-30 on, the specific death rate from diseases of the circulatory system and related organs increases at an almost absolutely constant rate until age 85 is reached. After that, the rate of increase slows down somewhat. Of those reaching the ages 95-100, between 70 and 80 out of each thousand living die from breakdown of this group of organs.

The specific mortality curve for deaths from breakdown of the respiratory system, as shown in Figure 29, presents a number of points of peculiar interest. In the first place we note that this organ system is much more liable to breakdown than is the circulatory system during all the earlier years of life up to about age 60-65. The decline in the curve from the high point of infancy to the low point of the period about puberty is more sharp and sudden than that of the circulatory system curve. Again, however, just as in the former case, we note that the specific force of mortality from breakdown of this organ system impinges more heavily upon females than upon

males in the years from 5-20. This difference is probably connected, as before, with the greater physiological disturbance of puberty in the female than in the male.

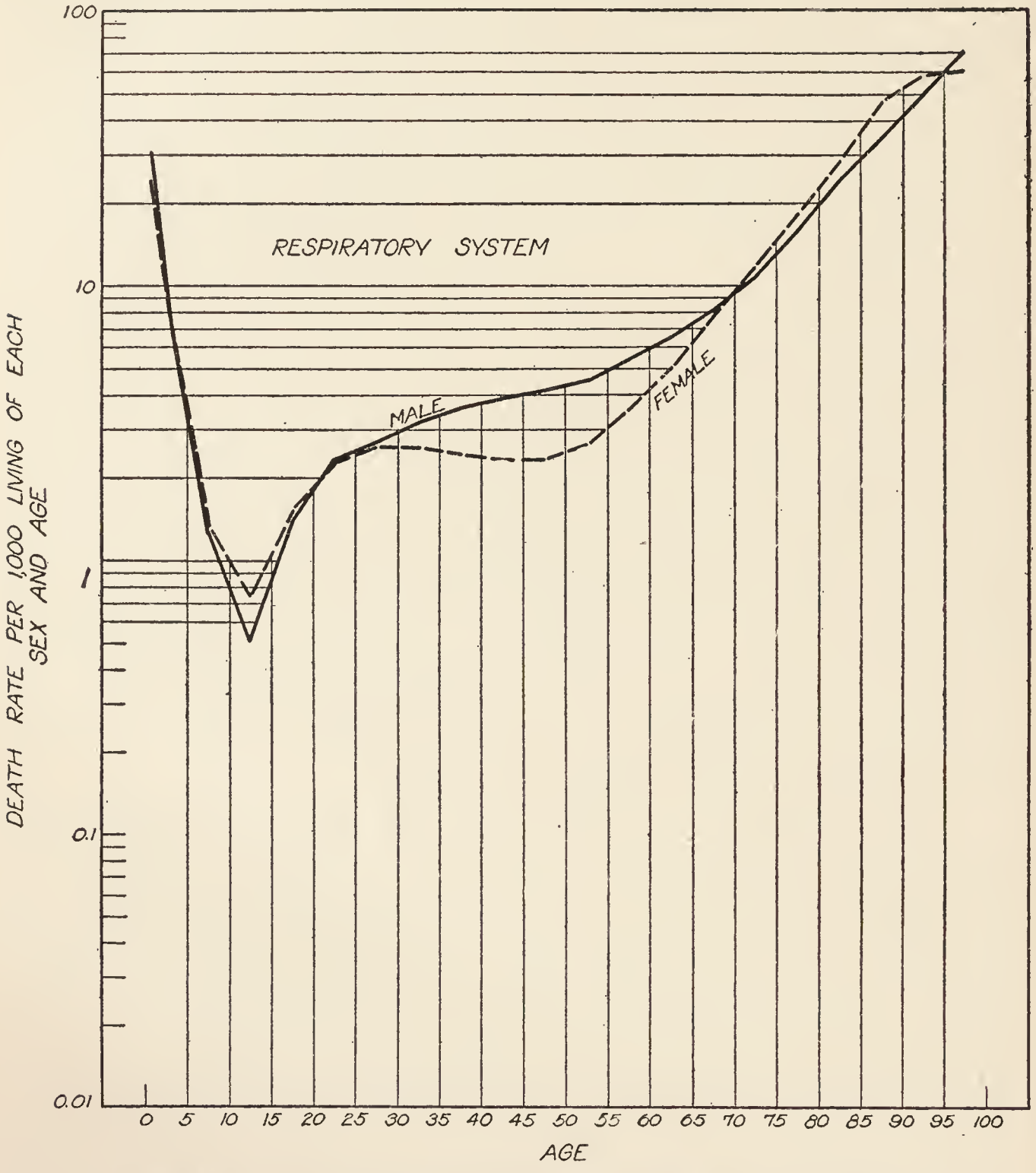


Fig. 29.—Diagram showing the specific death rate at each age from breakdown of the respiratory system (Group II).

The lowest point of the respiratory curve falls in the age group 10-15. Between the ages 25-70 there is a very striking difference in the two sexes in respect of specific

mortality from breakdown of the respiratory system. The male curve rises in nearly a straight line, while the female curve lies far below it, and actually shows a point of inflection at about age 45, becoming for a short period convex to the base. The explanation for the great separation of the two curves in this period is probably fundamentally occupational. From the nature of their activity males, during this period of life, are probably subject to a greater risk of breakdown of the respiratory system than are the more protected female lives. From age 70 on, both curves ascend with increased rapidity, the female curve rising above the male, presumably in compensation for the marked dip which it exhibits in middle life. It is, of course, well known that respiratory mortality bears heavily upon the aged.

The next group which we shall consider has to do with deaths from breakdown of the primary and secondary sex organs. This cause group furnishes an extremely interesting pair of curves shown in Figure 30. Before discussing in detail their form, a word of explanation as to their makeup should be given. This may best be done by exhibiting and discussing for a moment the causes of death which are included in this group. Table 10 shows the data.

In this rubric are included "Premature birth" and "Injuries at birth." The question at once arises, why should these two items, "Premature birth" and "Injuries at birth" be included with the primary and secondary sex organs, since it is obvious enough that the infants whose deaths are recorded under these heads in the vast majority of cases, if not all, have nothing whatever the matter with either their primary or secondary organs? The answer is, in general terms, that on any proper biological

basis, death coming under either of these two categories is not properly chargeable, organically, against the infant at

TABLE 10

Primary and secondary sex organs

No.	"Cause of Death" as per International Classification	Registration Area, U. S. A.		England and Wales 1914	São Paulo 1917
		1906–10	1901–05		
151*	Premature birth	35.7	30.8	46.9	66.8
42	Cancer of the female genital organs	10.8	10.0	12.9	6.5
137	Puerperal septicemia	6.8	6.3	3.7	6.5
152*	Injuries at birth	6.6	5.0	2.8	2.1
43	Cancer of the breast	6.5	5.6	10.4	1.5
37	Syphilis	5.4	4.1	5.8	15.0
126	Diseases of the prostate	3.4	2.6	4.2	0.7
132	Salpingitis and other diseases of ♀ genital organs	2.2	2.1	0.5	0.2
129	Uterine tumor (non-cancerous)	1.8	1.8	0.8	0
134	Accidents of pregnancy	1.7	1.7	1.1	0.2
130	Other diseases of the uterus	1.6	1.7	0.4	0.4
136	Other accidents of labor	1.3	0.9	1.1	0.7
140	Following childbirth	1.1	1.5	0.1	—
131	Cysts and other tumors of ovary	1.0	1.3	0.8	0.2
135	Puerperal hemorrhage	1.0	1.0	1.3	1.7
125	Diseases of the urethra, urinary abscesses, etc.	0.4	0.4	1.2	0.7
38	Gonococcus infection	0.3	0.1	0.2	0
128	Uterine hemorrhage (non-puerperal)	0.2	0.3	0	0
127	Non-venereal diseases of ♂ genital organs	0.1	0.1	0.2	0
133	Non-puerperal diseases of breast (except cancer)	0.1	0.1	0.1	0
139	Puerperal phlegmasia, etc.	0.1	—	0.9	0
	Totals	88.1	77.4	95.4	103.2

* In part.

all, but should be charged, on such a basis, against the mother. To go further into detail, it is apparent that when a premature birth occurs it is because the reproductive

system of the mother, for some reason or other, did not rise to the demands of the situation of carrying the fœtus to term. Premature birth, in short, results from a failure or breakdown in some particular of the *maternal reproductive system.* This failure may be caused in various ways, which do not here concern us. The essential feature from our present viewpoint is that the reproductive system of the mother does break down, and by so doing causes the death of the infant, and that death is recorded statistically under this title "Premature birth." The death organically is chargeable to the mother.

A considerable number of cases of premature birth are unquestionably due to placental defects and the placenta is a structure of fœtal origin, so such deaths could not be properly charged to the mother. On the other hand, however, they would still stay in the same table because the placenta may fairly be regarded as an organ intimately concerned in reproduction.

The same reasoning which applies to premature births, *mutatis mutandis,* applies to the item "Injuries at birth." An infant death recorded under this head means that some part of the reproductive mechanism of the mother, either structural or functional, failed of normal performance in the time of stress. Usually "injury at birth" means a contracted or malformed pelvis of the mother. But in any case the death is purely external and accidental from the standpoint of the infant. It is organically chargeable to a defect of the sex organs of the mother. The female pelvis, in respect of its conformation, is a secondary sex character.

The immediate reason for including syphilis and gonococcus infection here is obvious, but, particularly in relation to syphilis, the point needs further discussion.

As a cause of actual death, syphilis frequently acts through the central nervous system, and the question may fairly be raised why, in view of this fact, syphilis is not tabled there. The point well illustrates one of the fundamental difficulties in any organological classification of disease. In the case of syphilis, however, the difficulty in practice is not nearly so great as it is in theory. As a matter of fact, most of the deaths from the effect of syphilitic infection on the nervous system are recorded in vital statistics by reporting physicians and vital statisticians as diseases of the nervous system. For example, it is perfectly certain that most of the deaths recorded as due to "locomotor ataxia" are fundamentally syphilitic in origin. The rate of 5.4 for the Registration Area of the United States in 1906-10 for deaths due to syphilis is far lower, as any clinician knows, than the number of deaths really attributable to syphilitic infection. These other deaths, due to syphilis, and not reported under that title, are reported under the organ which primarily breaks down and causes death, as, for example, the brain, and will in the present system of classification be included under the nervous system. After careful consideration, it has seemed as fair as anything which could be done to put the residue of deaths specifically reported as due to syphilis under Primary and Secondary Sex Organs. The rate, in any event, is so small that whatever shift was made could not sensibly affect the general results to which we shall presently come.

Turning now to the consideration of Figure 30, which gives the curves of specific mortality from breakdown of the reproductive organs, we note at once the high specific death rate of infants under one, recorded by the female line. This rate is over 40 per thousand exposed to risk.

It includes, of course, both male and female infants, dying from congenital debility, premature birth and injuries at birth, because, according to the reasoning just explained,

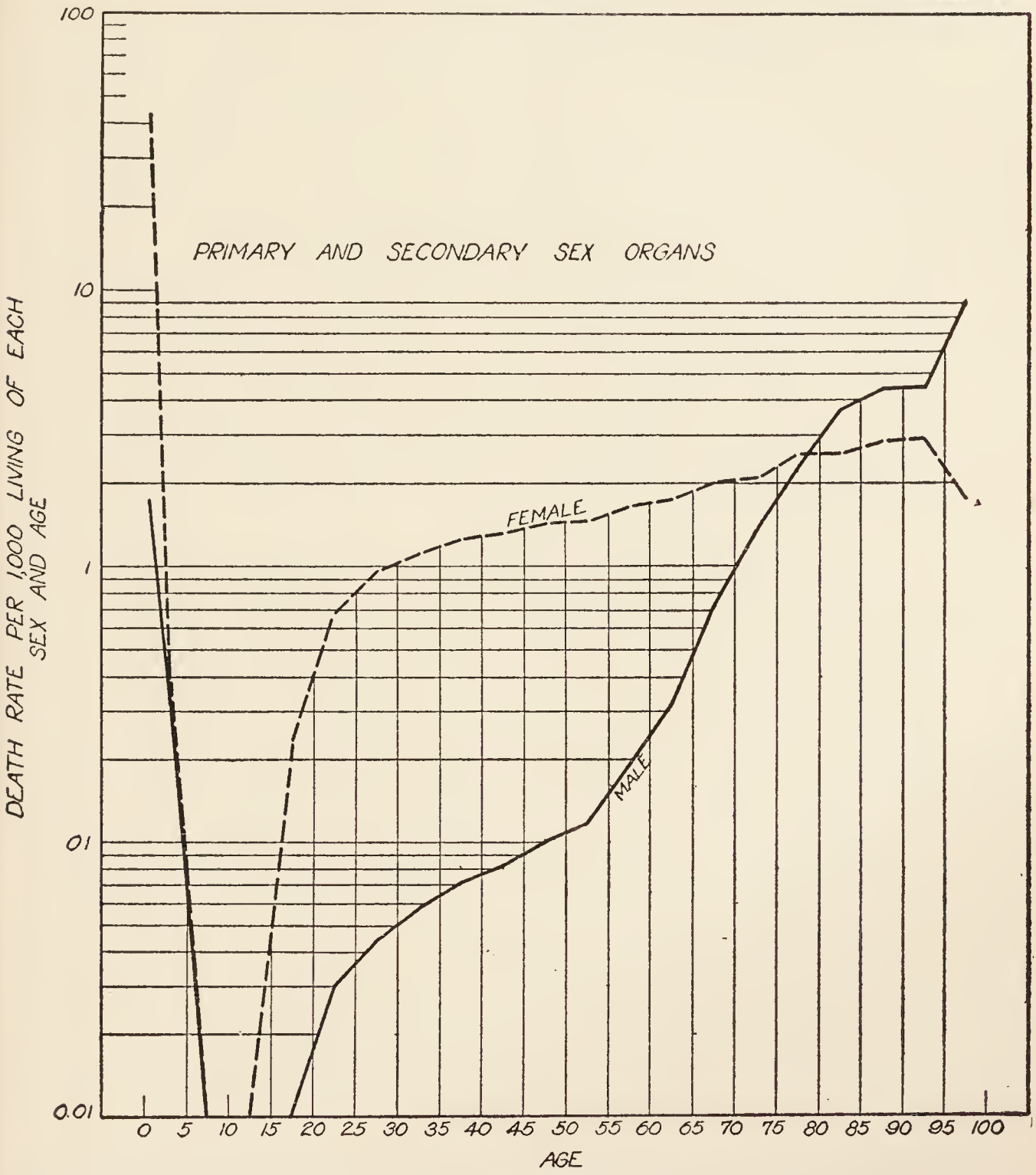


FIG. 30.—Diagram showing specific death rates at each age from breakdown of the primary and secondary sex organs (Group III).

these deaths are organically chargeable to breakdown or failure to function properly of the reproductive organs of the mother. These deaths, therefore, go into the

female group. By the fifth year of life, the specific rates of mortality chargeable to reproductive organs have dropped in both sexes practically to zero, amounting to less than 0.01 per thousand exposed to risk. At about the time of puberty the female curve begins to rise and goes up very steeply. By age 30 it has reached a value of 1 per thousand exposed to risk. From that point the force of this specific mortality rises slowly, but at a practically constant rate, to extreme old age. The male curve is in striking contrast to the female. From about age 20 it rises steadily, at an almost constant rate of increase, but a much slower one than the female, until the end of the life span. It crosses the female curve—indicating a higher specific rate of mortality from breakdown of the reproductive organs in men than in women—for the first time at about age 78. This is, of course, the time of life when disturbed functioning of the prostate gland in the male begins to take a relatively heavy toll.

Figure 31 shows specific rates of mortality from breakdown of the kidneys and related excretory organs. Death from these causes is relatively infrequent in infancy and early childhood. The low point is reached, as in so many of the other cases, at about the time of puberty. From then on practically to the end of the span of life the specific force of mortality from excretory failure increases at an almost constant rate. During the reproductive period, from about 15 to 45 years of age, specific rates of mortality from these causes are higher in the female than in the male. After that point the male curve is higher. The relatively heavy specific mortality of the female in early life is undoubtedly due to the heavy strain put upon her excretory organs by child-bearing.

The specific force of mortality from breakdown of

the skeletal and muscular systems, shown in Figure 32, presents an interesting pair of curves. Throughout the span of life there is practically no difference between

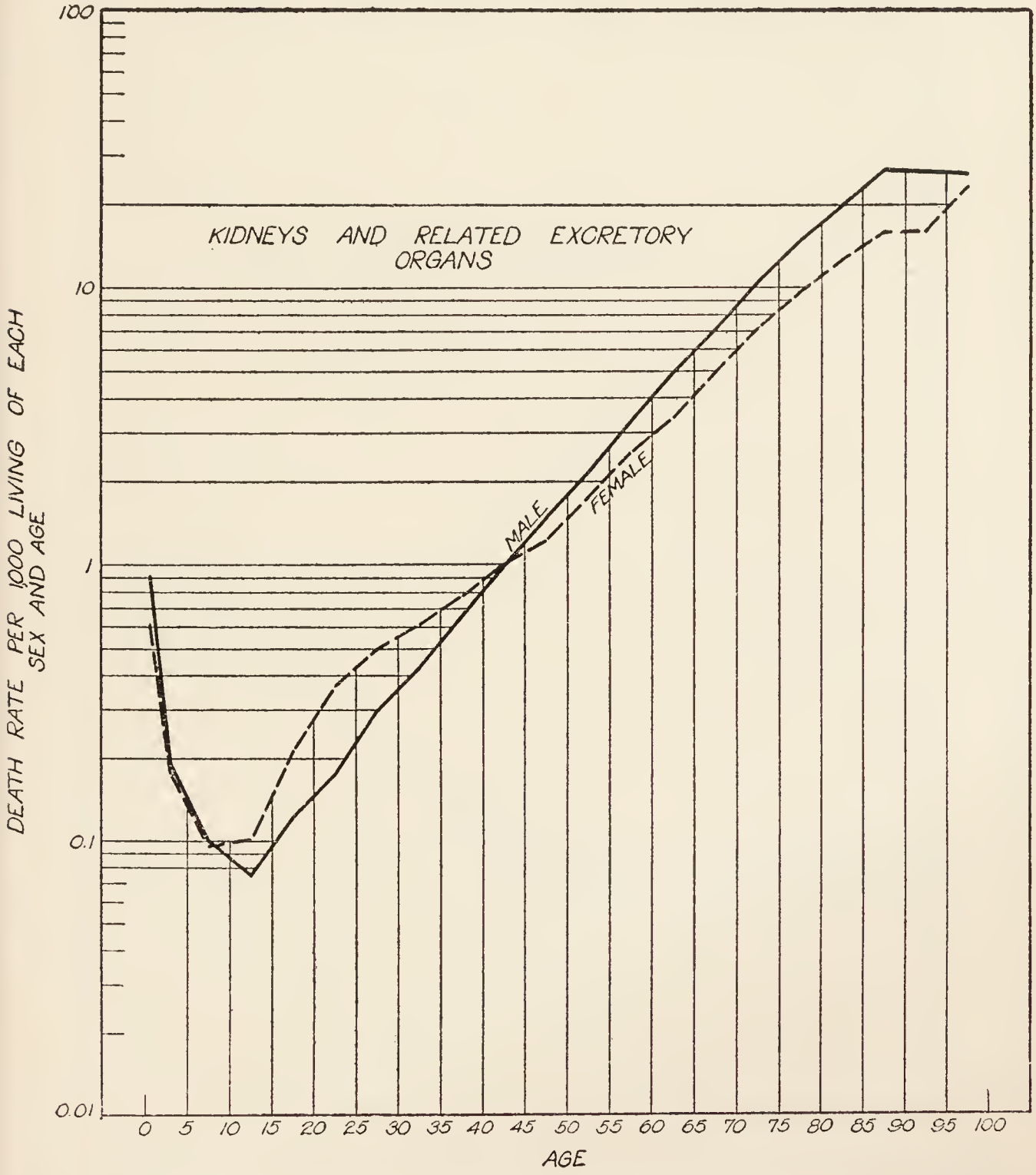


Fig. 31.—Diagram showing specific death rates at each age from breakdown of the kidneys and related excretory organs (Group IV).

the female and male in the incidence of this mortality, the curves winding in and out about each other. The striking characteristics of the curve are: first, that the specific forces of mortality are absolutely low for these

organ systems; and second, that the minimum point is reached not, as in most of the other cases, around the time of puberty, but at a much later period—namely in the

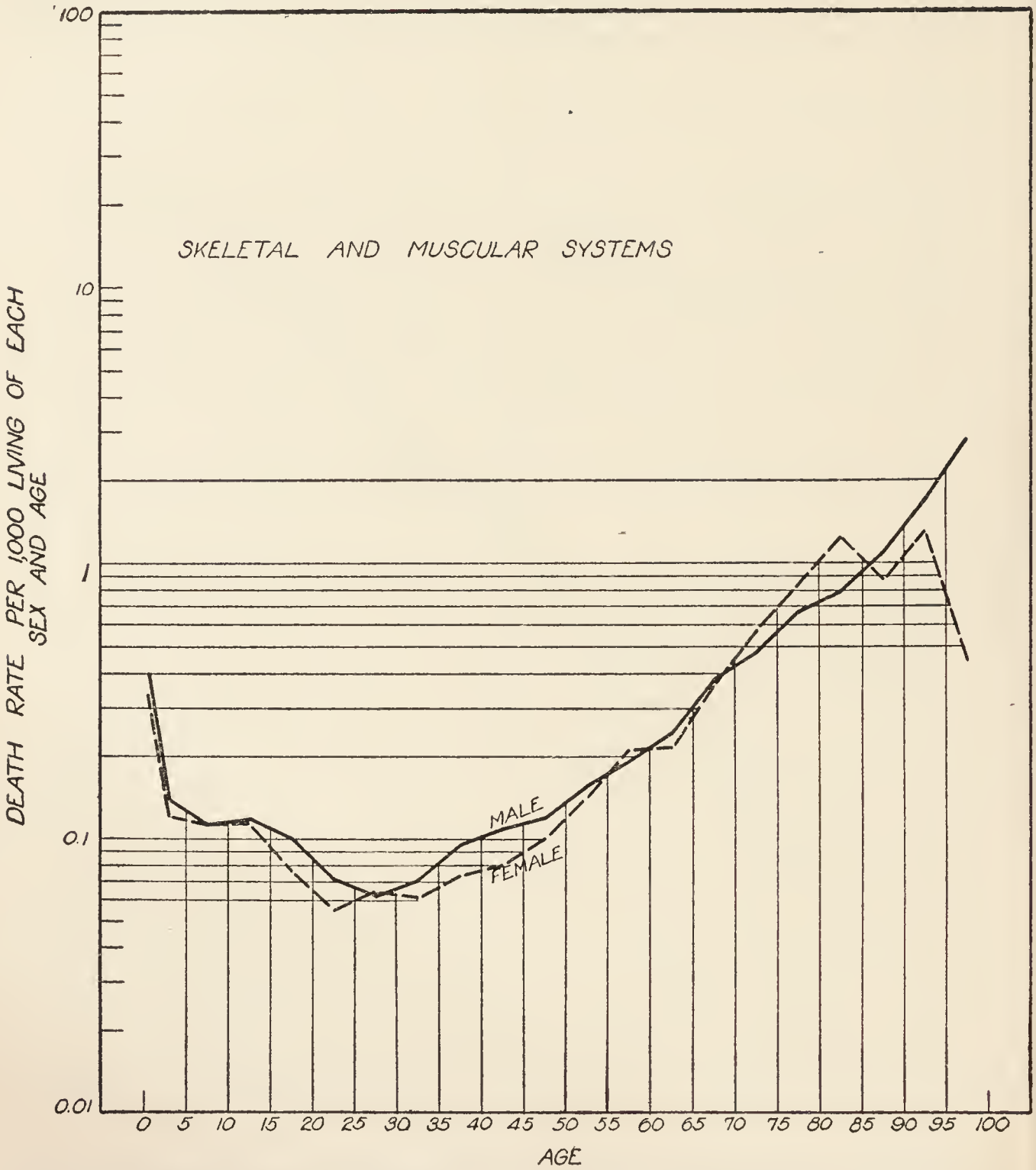


FIG. 32.—Diagram showing specific death rates at each age from breakdown of the skeletal and muscular systems (Group V).

late twenties. The whole curve shows a very gradual change in the rates.

The next diagram, Figure 33, shows one of the most

significant organ groups in the force of its specific mortality. Breakdown and failure to function properly of the primary organs of metabolism—the organs which

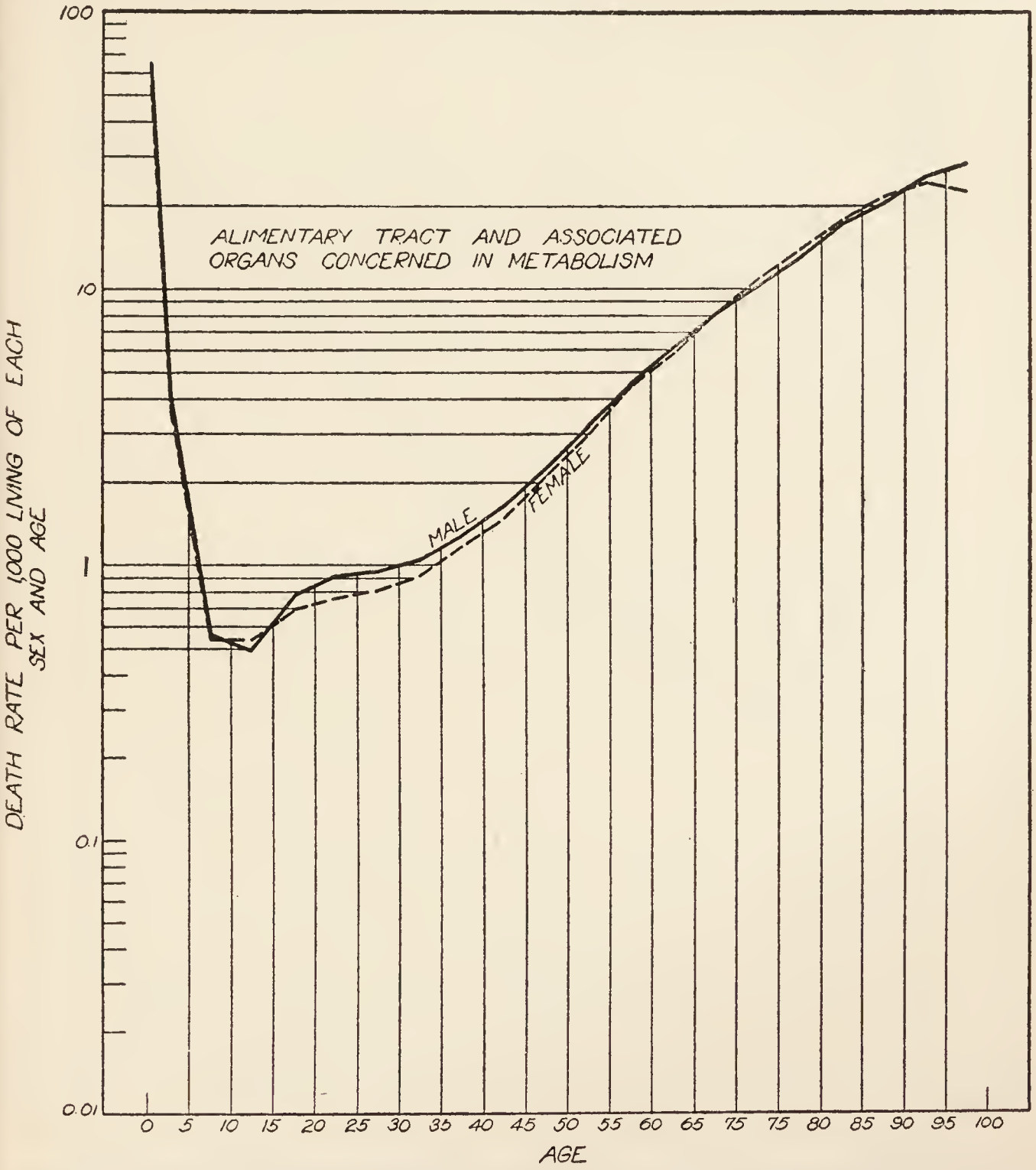


FIG. 33.—Diagram showing the specific rates of death at each age from breakdown of the alimentary tract and associated organs of metabolism (Group VI).

transform the fuel of the human machine into vital energy —occur with relatively heavy frequency at all periods of life. These curves are among the few which show an

absolutely higher specific force of mortality in infancy than in extreme old age. There is practically no significant difference between the male and female curve at

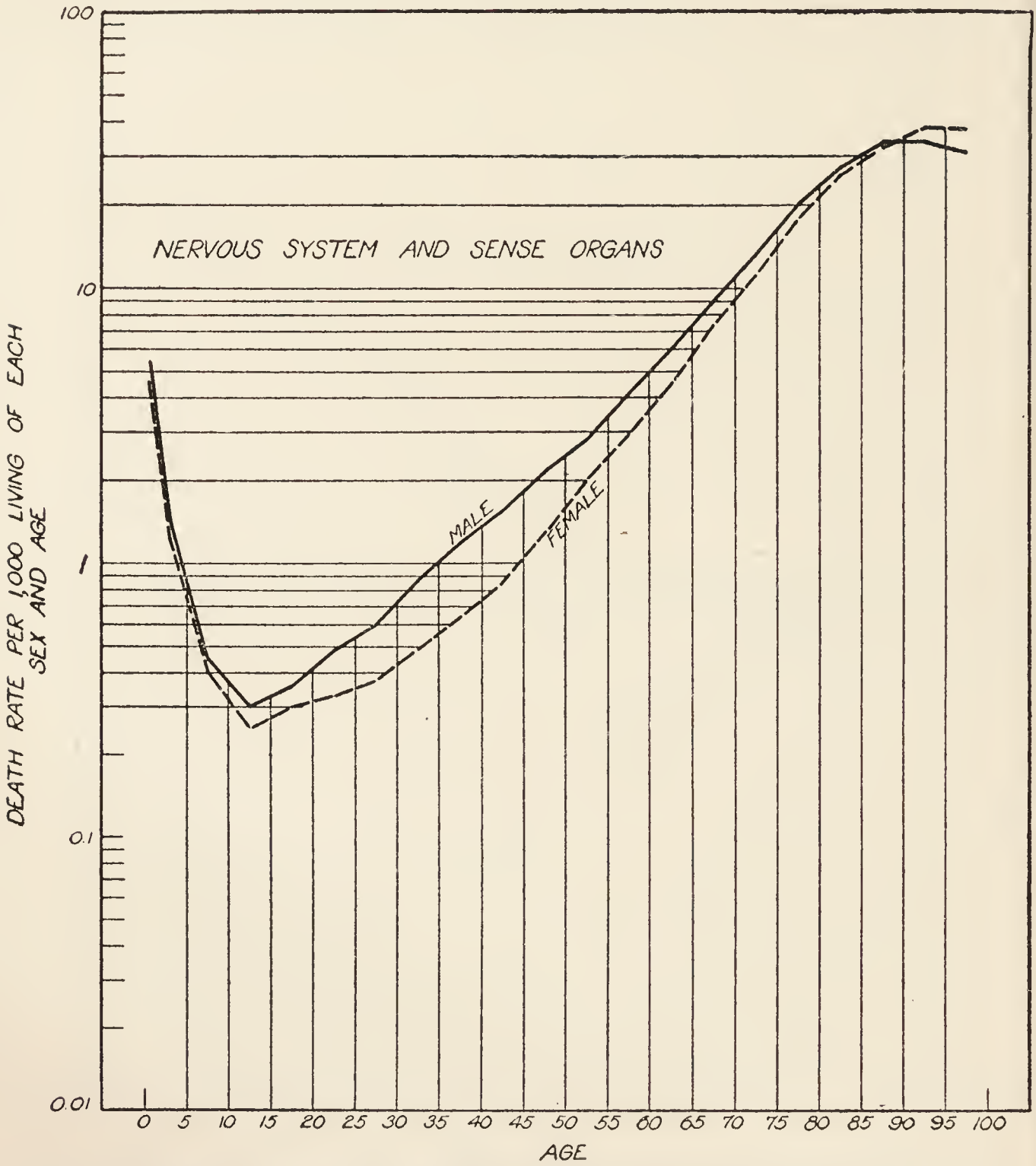


FIG. 34.—Diagram showing the specific death rates at each age from breakdown of the nervous system and sense organs (Group VII).

any portion of life. During early adult life the female curve lies below the male, but by only a small amount. Out of every thousand infants under one, about sixty

die in the first year of life from breakdown of the alimentary tract and its associated organs. After the low point, which falls in the relatively early period of 7 to 12 years of age, there is a rapid rise for about ten years in the specific rates of mortality, followed by a slowing off in the rate of increase for the next ten or fifteen years, after which point the curve ascends at a practically uniform rate until the end of the span of life.

Figure 34 shows the trend of the specific mortality from breakdown of the nervous system and sense organs. This organ group, on the whole, functions very well, giving a relatively low rate of mortality until towards the end of middle life. Then the specific rates get fairly large. The low point in this curve is, as in most of the others, at about the time of puberty. From then on to the end of the life span the specific rates increase at a practically uniform rate. The female curve everywhere lies below the male curve except at the extreme upper end of the life span. Before that time, and particularly between the ages of 20 and 50, the business of living evidently either imposes no such heavy demand on the nervous system of the female as it does on that of the male, or else the nervous system of the female is organically sounder than that of the male. The former suggestion seems the more probable.

That breakdown and failure to function properly, of the skin as an organ system, is a relatively insignificant factor in human mortality, is demonstrated by Figure 35. From a specific death rate of about 1 per thousand in the first year of life it drops abruptly, practically to zero, in early childhood. At about the time of puberty it begins to rise again, and ascends at a steady rate during all the remainder of life. The final high point reached

is absolutely low, however, amounting to a specific death rate among those exposed to risk of only a little more than 4 per thousand at the extreme end of life. The female

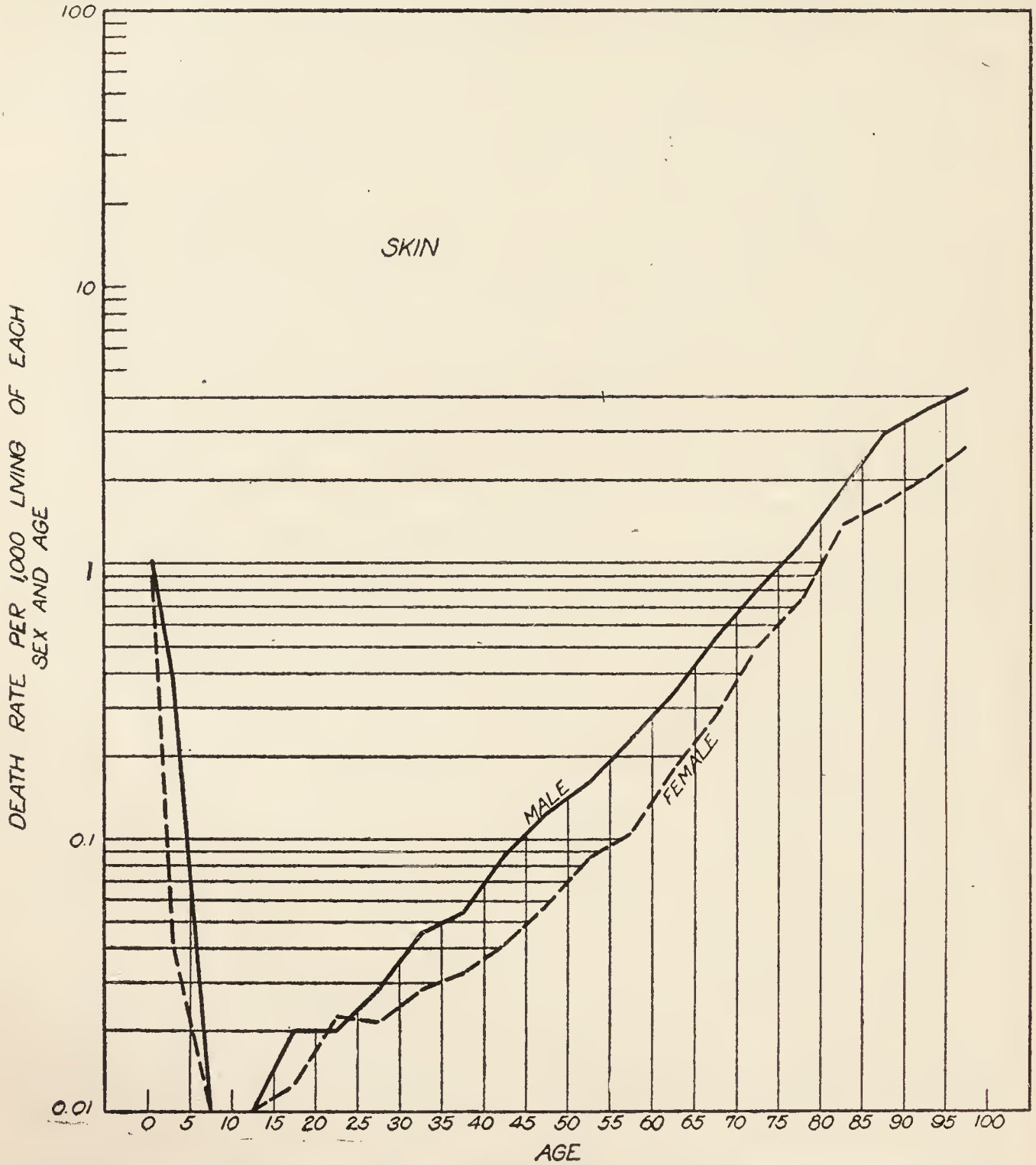


FIG. 35.—Diagram showing the specific death rates at each age chargeable against the skin (Group VIII).

curve lies well below the male curve practically throughout its course.

Deaths from failure to function properly of the organs

of the endocrinal system, including the thyroid gland, suprarenal glands, etc., do not become significant until middle life in the case of the male, as shown in Figure 36,

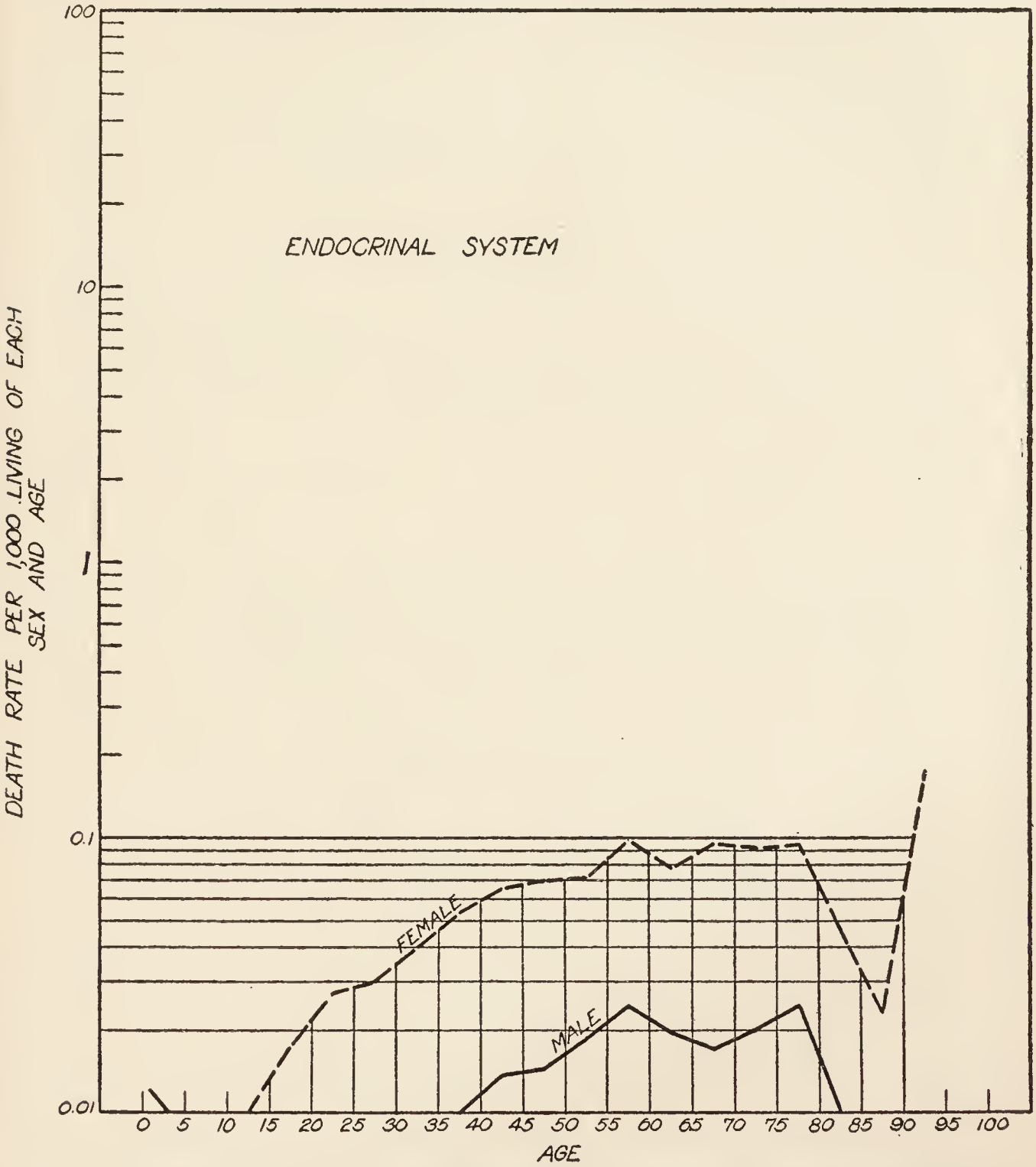


Fig. 36.—Diagram showing the specific death rates at each age from breakdown of the endocrinal system (Group IX).

although in the female the curve begins to rise from puberty on. The specific rates at all ages, of course, are extremely small, practically never rising to more than

1/10 of one person per thousand exposed to risk. The well-known fact that these glandular organs, whose secretions are so important for the normal conditions of

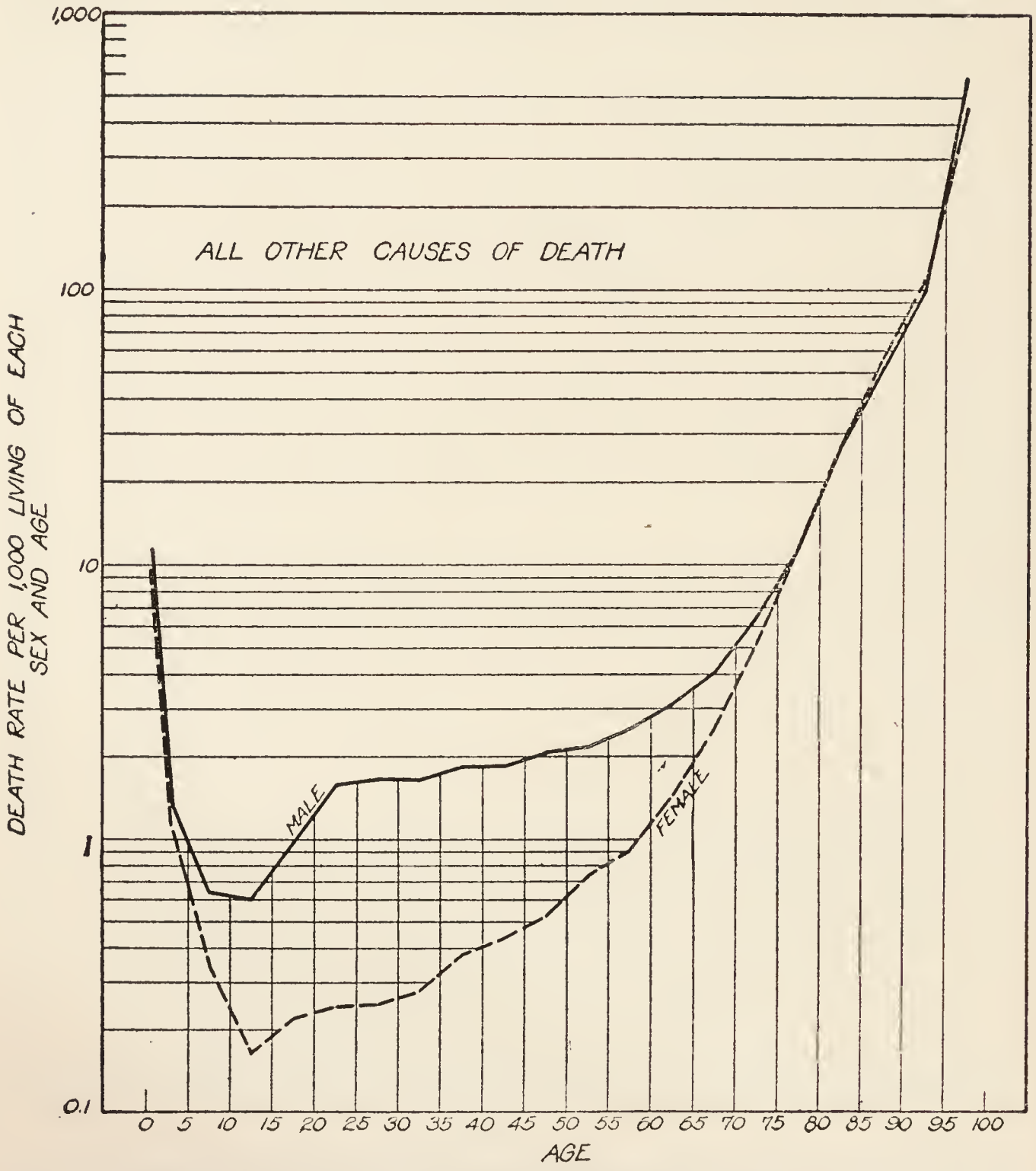


FIG. 37.—Diagram showing the specific death rates from all other causes of death not covered in the preceding categories (Group X).

life, are much more unstable and liable to breakdown in the female than in the male, is strikingly shown by this diagram.

Finally, we have the diagram for our *omnium gatherum* group, the "All other causes of death," in Figure 37. Here we see that, because of accidental and violent deaths, the male specific mortality curve lies far above the female, from youth until old age has set in, about age 75. From that point on to the end of the span of life both curves ascend rapidly together, as a result of the deaths recorded as resulting from senility. Eventually it is to be expected that no deaths will be registered as resulting from senility. We shall have them all put more nearly where they belong.

These diagrams of specific forces of mortality give altogether a remarkably clear and definite picture of how death occurs among men. We see that failure of certain organ systems, such as the lungs, the heart, the kidneys, to maintain their structural and functional integrity, has an overwhelmingly great effect in determining the total rate of mortality as compared with some of the other organ systems. One cannot but be impressed, too, with the essential orderliness of the phenomena we have examined. The probability of any particular organ system breaking down and causing death is mathematically definite at each age, and changes in a strikingly orderly manner as age changes, as is shown in Table 11. Thus we find that in the first year of life it is the alimentary tract and its associated organs which most frequently break down and cause death. From age 1 to age 60 the specific force of mortality from breakdown of the respiratory system is higher (with a few insignificant exceptions in the females) usually by a considerable amount, than that associated with any other organ system of the body. From 60 to 90 years of age the circulatory

system takes the front rank, with a higher specific mortality rate than any other organ system.

TABLE 11

The most fatal organ systems at different ages

MALES		Age Group	FEMALES	
Per cent. of all biologically classifiable deaths due to breakdown of specified organ system	Organ system concerned in largest proportion of fatalities		Organ system concerned in largest proportion of fatalities	Per cent. of all biologically classifiable deaths due to breakdown of specified organ system
68.8	Alimentary tract	0— 1	Alimentary tract	40.6
50.1	Respiratory	1— 4	Respiratory	51.3
41.2	Respiratory	5— 9	Respiratory	42.5
27.1	Respiratory	10—14	Respiratory	33.3
43.6	Respiratory	15—19	Respiratory	43.8
52.6	Respiratory	20—24	Respiratory	46.0
49.7	Respiratory	25—29	Respiratory	44.2
45.6	Respiratory	30—34	Respiratory	39.5
39.9	Respiratory	35—39	Respiratory	33.2
33.3	Respiratory	40—44	Respiratory	27.5
28.0	Respiratory	45—49	Respiratory	22.1
23.6	Respiratory	50—54	Alimentary tract	21.6
25.0	Circulatory	55—59	Alimentary tract	22.6
28.4	Circulatory	60—64	Circulatory	24.4
30.9	Circulatory	65—69	Circulatory	25.6
32.5	Circulatory	70—74	Circulatory	28.0
32.9	Circulatory	75—79	Circulatory	28.4
33.3	Circulatory	80—84	Circulatory	30.4
		85—89	Circulatory	30.8

If our lungs were as organically good relatively as our hearts, having regard in each case for the work the organ is called upon to do and the conditions under which it must do it, we should live a considerable number of years longer on the average than we do now. One cannot but feel that the working out of a rational and scientifically grounded system of personal hygiene of the respir-

atory organs, on the broadest basis, to include all such matters as ventilation of buildings, etc., and the putting of such a personal hygiene into general use through education, would pay about as large dividends as could be hoped for from any investment in public health securities. I am aware that much has already been done in this direction, but in order to reap any such dividends as I am thinking of, a vast amount must be added to our present knowledge of the physiology, pathology, epidemiology, and every other aspect of the functions and structures of respiration.

CHAPTER V

EMBRYOLOGY AND HUMAN MORTALITY

In the preceding chapter attention was confined strictly to the organological incidence of death. It is possible to push the matter of human mortality still farther back. In the embryological development of the vertebrate body, there are laid down at an early stage, in fact immediately following the process of gastrulation, three morphologically definite primitive tissue elements, called respectively the ectoderm, the mesoderm and the endoderm. These are termed the germ-layers, and embryological science has, for a great many forms, succeeded in a broad way in tracing back to the primitive germ layer from which it originally started its development, substantially every one of the adult organs and organ systems of the body. It makes no difference to the validity or significance of the discussion which we are about to enter upon, in what degree of esteem or contempt in biological philosophy the germ layer theory or doctrine, which occupied so large a place in morphological speculation 50 years ago, may be held. We are here concerned only with the well-established broad descriptive fact, that in general all adult organ systems may be traced back over the path of their embryological development to the germ layer, or combination of germ layers, from which they originally started.

Having arranged, so far as possible, all causes of death on an organological basis, it occurred to me to go one

step further back and combine them under the headings of the primary germ layers from which the several organs developed embryologically. To do this was a task of considerable difficulty. It raised intricate, and in some

TABLE 12

Showing the relative influence of the primary germ layers in human mortality
(Items 64 and 65 charged to ectoderm)

Locality	Death rate per 100,000 due to functional breakdown of organs embryologically developing from					
	Ecto-derm	Per cent.	Meso-derm	Per cent.	Endo-derm	Per cent.
United States Registration Area, 1906–10	191.1	14.3	425.2	31.8	719.6	53.9
United States Registration Area, 1901–05	210.6	15.0	407.1	29.0	786.2	56.0
England and Wales, 1914	177.1	14.4	374.0	30.3	681.5	55.3
Sao Paulo, 1917	134.9	8.4	468.0	29.0	1009.9	62.6

TABLE 13

Showing the relative influence of the primary germ layers in human mortality
(Items 64 and 65 charged to mesoderm)

Locality	Death rate per 100,000 due to functional breakdown of organs embryologically developing from					
	Ecto-derm	Per cent.	Meso-derm	Per cent.	Endo-derm	Per cent.
United States Registration Area, 1906–10	116.9	8.7	499.4	37.4	719.6	53.9
United States Registration Area, 1901–05	137.3	9.8	480.4	34.2	786.2	56.0
England and Wales, 1914	107.9	6.7	443.2	36.0	681.5	55.3
Sao Paulo, 1917	101.3	6.3	501.6	31.1	1009.9	62.6

cases still unsettled, questions of embryology. Furthermore, the original statistical rubrics under which the data are compiled by registrars of vital statistics were never planned with such an object as this in mind. Still the thing seemed worth trying because of the biological interest which would attach to the result, even though it were some-

what crude and, in respect of minor and insignificant details, open to criticism. It is not possible here to go into details as to how the causes of death were combined in

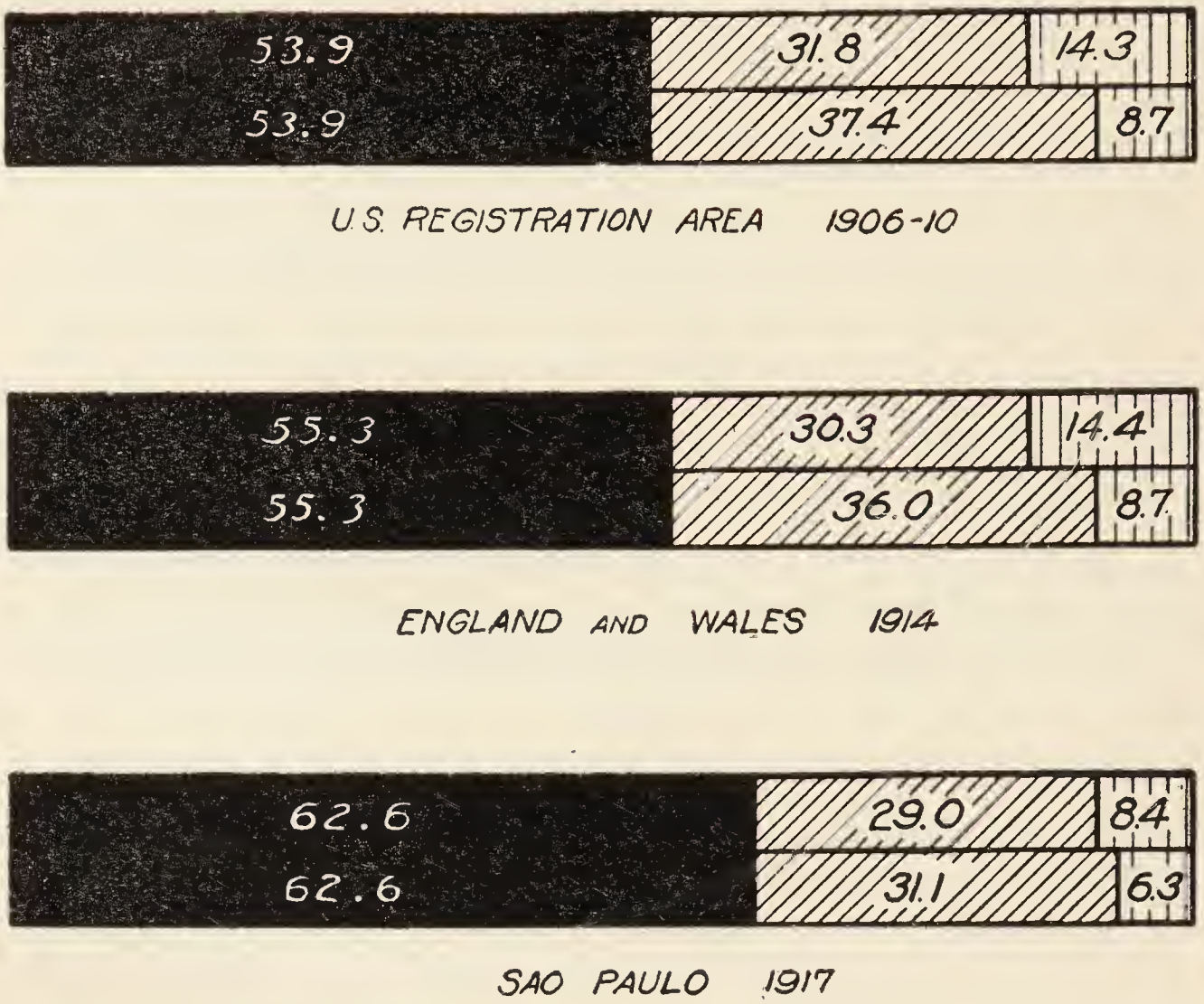


FIG. 38.—Diagram showing the percentages of biologically classifiable human mortality resulting from breakdown of organs developing from the different germ layers. Upper bar of pair gives upper limit of mortality chargeable to ectoderm: lower bar gives lower limit of mortality chargeable to ectoderm.

making up the final tables. For these details one must refer to the original papers.

Tables 12 and 13, and Figure 38, give the results for the crude mortality of the U. S. Registration Area, England and Wales, and Sao Paulo, Brazil.

The figures show that in man, the highest product of organic evolution, about 57 per cent. of all the biologically classifiable deaths result from a breakdown and failure further to function of organs arising from the endoderm in their embryological development, while but from 8 per cent. to 13 per cent. can be regarded as a result of breakdown of organ systems arising from the ectoderm. The remaining 30 to 35 per cent. of the mortality results from failure of mesodermic organs. The two values stated for ectoderm and mesoderm, shown by the two bars in the diagram, differ by virtue of the fact that two important causes of death, cerebral hemorrhage and apoplexy, and softening of the brain, are put in the one case with the ectoderm and in the other case with the mesoderm. The pathological arguments for the one disposition as against the other of these two diseases are interesting, but lack of space prevents their exposition here. I have chosen rather to present the facts in both ways.

Taking a general view of comparative anatomy and embryology it is evident that in the evolutionary history through which man and the higher vertebrates have passed it is the ectoderm which has been most widely differentiated from its primitive condition, to the validity of which statement the central nervous system furnishes the most potent evidence. The endoderm has been least progressively changed structurally and functionally in the process of evolution, while the mesoderm occupies, on the whole, an intermediate position in this respect.

Degree of differentiation of organs in evolution implies degree of adaptation to environment. From the present point of view we see that the germ layer, the endoderm, which has evolved or become differentiated least in

the process of evolution is least able to meet successfully the vicissitudes of the environment. The ectoderm has changed most in the course of evolution. Of this the central nervous system of man is the best proof. There have also been formed in the process of differentiation, protective mechanisms, the skull and vertebral column, which very well keep the delicate and highly organized central nervous system away from direct contact with the environment. The skin also exhibits many differentiations of a highly adaptive nature to resist environmental difficulties. It is then not surprising that the organ systems developed from the ectoderm break down and lead to death less frequently than any other. The figures make it clear that man's greatest enemy is his own endoderm. Evolutionally speaking, it is a very old-fashioned and out-of-date ancestral relic, which causes him an infinity of trouble. Practically all public health activities are directed towards overcoming the difficulties which arise because man carries about this antediluvian sort of endoderm. We endeavor to modify the environment, and soften its asperities down to the point where our own inefficient endodermal mechanism can cope with them, by such methods as preventing bacterial contamination of water, food and the like, warming the air we breathe, etc. But our ectoderm requires no such extensive amelioration of the environment. There are at most only a very few, if any, germs which can gain entrance to the body through the normal, healthy unbroken skin. We do, to be sure, wear clothes. But it is at least a debatable question whether, upon many parts of the earth's surface, we should not be better off without them from the point of view of health.

These data indicate further in another manner how

important are the fundamental embryological factors in determining the mortality of man. Of the three localities compared, England and the United States may be fairly regarded as much more advanced in matters of public health and sanitation than São Paulo. This fact is reflected with perfect precision and justice in the relative proportion of the death rates from endoderm and ectoderm. In the United States and England about 55 per cent. of the classifiable deaths are chargeable to endoderm and about 9 to 14.5 per cent. to ectoderm. In São Paulo 62.6 per cent. fall with the endoderm, and but 6.3 to 8.4 per cent. with the ectoderm. Since public health measures can and do affect practically only the death rate chargeable to endoderm, this result, which is actually obtained, is precisely that which would be expected.

A question which naturally occurs is as to what the age distribution of breakdown of ectodermic, mesodermic, or endodermic organs may be. Are the endodermic organs, for example, relatively more liable to breakdown in early life, and less so later, as general observation would lead one to conclude?

To answer this and similar questions which come to mind it is necessary to distribute the specific rates of Table 9 upon an embryological basis.

In Figure 39 the result of doing this is shown for males. We note that prior to age 60 the curve for the breakdown of organs of endodermic origin lies at the top of the diagram; next below it comes the curve for the breakdown of organs of mesodermic origin; and finally at the bottom the curve for the breakdown of organs of ectodermic origin. All three of the curves have in general the form of a specific death rate curve. The rates for all three germ layers are relatively high in in-

fancy and drop at a practically constant rate to a low point in early youth. In infancy the heaviest mortality in males is due to the breakdown of organs of endodermic

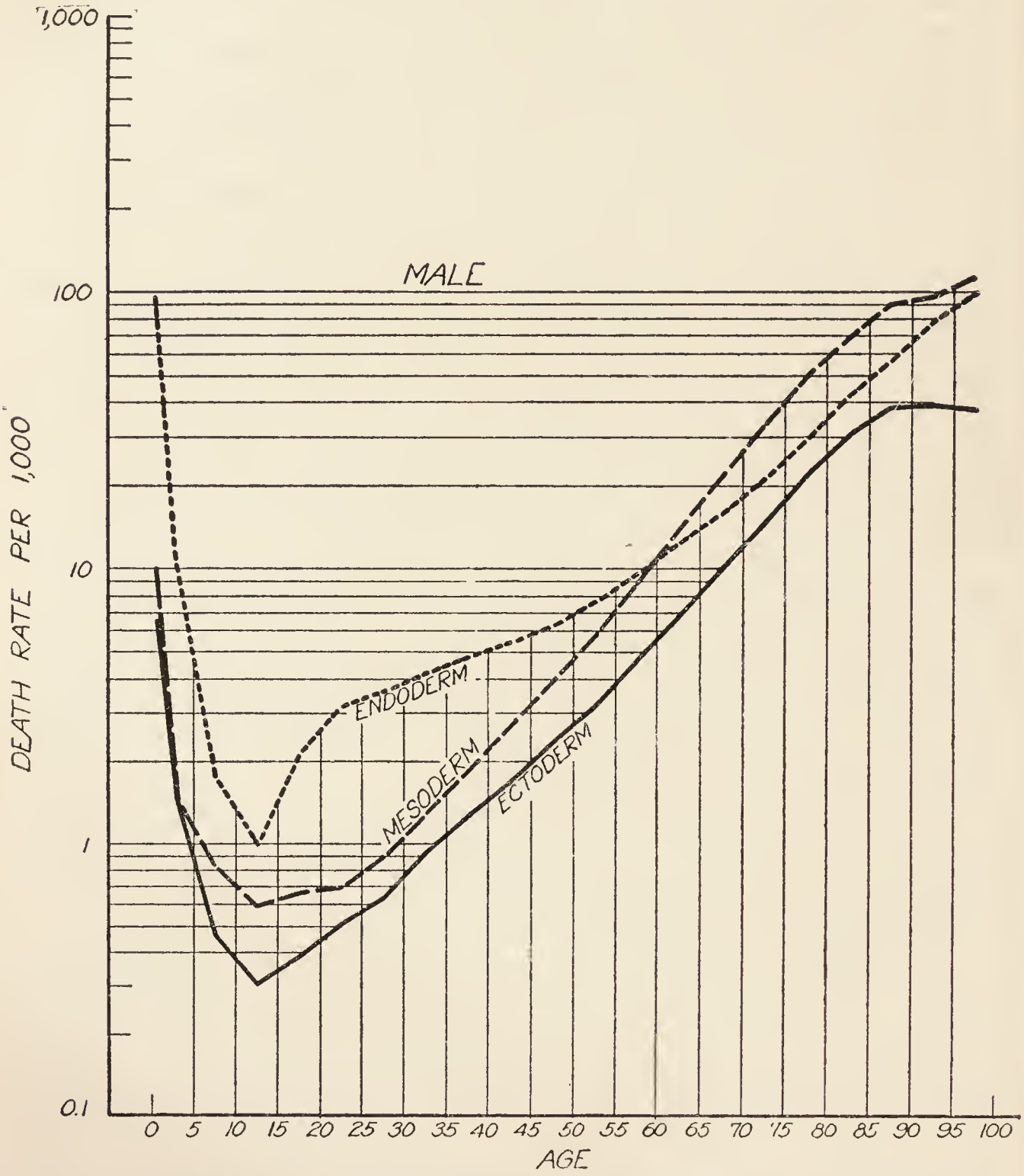


FIG. 39.—Showing specific death rates in males according to the germ layer from which the organs developed.

origin. This part of the death rate accounts for something like 10 times as many deaths as either mesoderm or ectoderm at this period of life. From about age 12 on in

the case of organs of ectodermic origin, and from about age 22 on in cases of mesodermic origin, the death rate curves rise at a practically constant rate to extreme old age. The ectodermic and mesodermic curves during this portion of the life span are nearly parallel, diverging only slightly from each other with advancing age. The curve for the death rate resulting from breakdown of organs of endodermic origin has an entirely different course. It rises sharply for ten years after the low point in early youth, and then makes a rather sharp bend at about age 22, and passes off to the end of the life span, at a reduced rate of change. In consequence of this it crosses the mesodermic line at age 60. From that point on to the end of life deaths from breakdown of organs of mesodermic origin stand first in importance.

Figure 40 shows the same set of facts for the female, and at once a number of striking differences between the conditions in the two sexes appear. In the first place, the breakdown of mesodermic organs is practically of equal importance in determining the mortality of infants with the breakdown of endodermic organs, in the case of the female. This fact, of course, arises because of the heavy mortality of infancy due to failure of the female reproductive organs, a matter which has already been discussed. The curve for breakdown of the ectodermic organs follows substantially the same kind of course in the female as it does in the male. The mesoderm and endoderm lines cross nearly 20 years earlier in the case of females than in the males. This circumstance arises from the fact that throughout life the mesodermic organs play a relatively more important rôle in the determination of mortality in the female than they do in the male.

What reward in the way of useful generalization may

be claimed from the details reviewed in this and the preceding chapter? I hope that these facts will have served in some measure to complete and round out in clearer

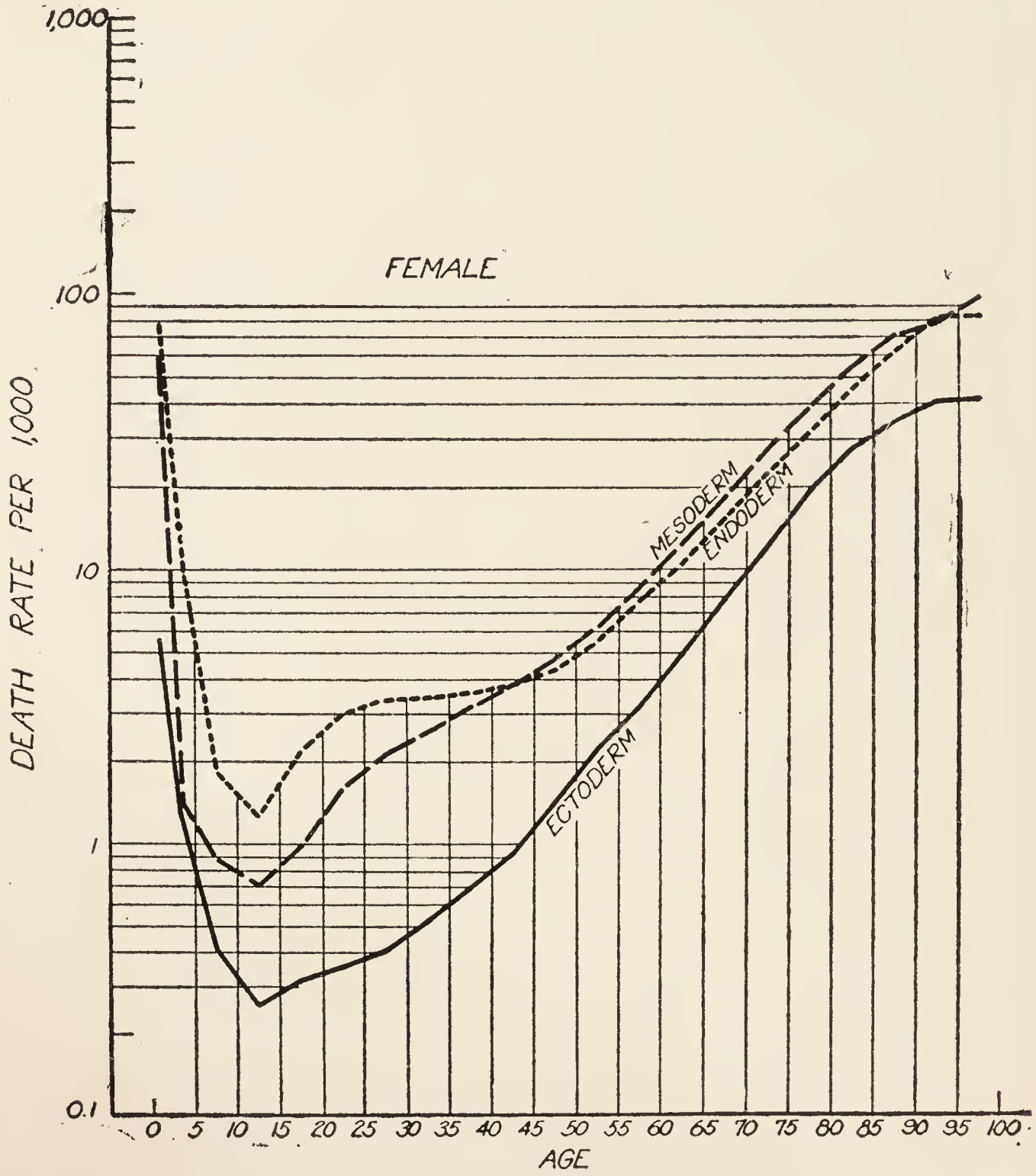


Fig. 40.—Showing specific death rates for females, classified in the same manner as in Fig. 39.

outlines one part of the picture of the general biology of death. It has been shown in what has preceded that natural death is not a necessary or inherent attribute or

consequence of life. Many cells are potentially immortal and the potentiality is actually realized if appropriate conditions are provided. Protozoa are immortal. Germ cells are immortal. Various somatic cells, and even tissues have been proved to be potentially immortal by demonstrating in a variety of ways that under appropriate conditions they continue to live indefinitely. This is the lesson taught us on the one hand by successive transplantations of tumor cells, which are only modified somatic cells, and on the other hand by successful culture of many sorts of somatic cells *in vitro*.

Analytical consideration of the matter shows very clearly that the somata of multicellular organisms die because of the differentiations and specializations of structure and function which they exhibit in their make-up. Certain cells are differentiated to carry on certain specialized functions. In this specialization they forego their power of independent and indefinitely continued existence. The cells lining the lungs, for example, must depend in the body upon the unfailing normal activity of the cells of the alimentary tract and the blood in order that they, the epithelial cells of the lungs, may get proper nutrition. If in such an interlocking and mutually dependent system any one part through accident or in any way whatever gets deviated from its normal functioning, the balance of the whole system is upset. If the departure of any part from its normal functional course is great enough to be beyond correction promptly through the normal regulatory powers of the organism, death of the whole will surely ensue.

What I have tried to show in this and the preceding chapter is a quantitative picture of how the different organ systems get out of balance, and wreck the whole

machine. The broad orderliness and lawfulness of the whole business of human mortality is impressive. We have seen that different organ systems have well-defined times of breakdown. Or, put in another way, we see that in the human organism, just as in the automobile, the serviceability of the different parts varies greatly. The heart outwears the lungs, the brain outwears both. But we have further, I believe, got an inkling of the fundamental reason why these things are so. It is broadly speaking, because evolution is a purely mechanistic process instead of being an intelligent one. All the parts are not perfected by evolution to even an approximately equal degree. It is conceivable that an omnipotent person could have made a much better machine, as a whole, than the human body which evolution has produced, assuming, of course, that he had first learned the trick of making self-regulating and self-reproducing machines, such as living machines are. He would presumably have made an endoderm with as good resisting and wearing qualities as the mesoderm or ectoderm. Evolution by the haphazard process of trial and error which we call natural selection, makes each part only just good enough to get by. In the very nature of the process itself it cannot possibly do anything any more constructive than this. The workmanship of evolution, from a mechanical point of view, is extraordinarily like that of the average automobile repair man. If evolution happens to be furnished by variation with fine materials, as in the case of the nervous system, it has no objection to using them, but it is equally ready to use the shoddiest of endoderm provided it will hold together just long enough to get the machine by the reproductive period.

It furthermore seems to me that the results presented

in this chapter add one more link to the already strong chain of evidence which indicates the highly important part played by innate constitutional biological factors as contrasted with environmental factors in the determination of the observed rates of human mortality. Here we have grouped human mortality into broad classes which rest upon a strictly biological basis. When this is done it is found that the proportionate subdivision of the mortality among the several causes—in short the death *ratios* in the sense of Fisher—is strikingly similar in such widely dissimilar environments as the United States, England and Southern Brazil.

CHAPTER VI

THE INHERITANCE OF DURATION OF LIFE IN MAN

We have seen that in the case of man, where alone quantitative data are available, the breakdown of particular organ systems, and consequent death of the whole, occurs in a highly orderly manner in respect of time or age. Each organ system has a characteristic time curve for its breakdown, differing from the curve of any other system. The problem which now confronts us is to find out what lies back of these characteristic time curves and determines their form. In view of the biological facts about death which we have learned, what determines that John Smith shall die at 58, while Henry Jones lives to the obviously more respectable age of 85? We have seen that there is every reason to believe that all the essential cells of both their bodies are inherently capable under proper conditions of living indefinitely. It further appears probable that it is the differentiated and specialized structure of their bodies which prevents the realization of these favorable conditions. But all this helps us not at all to understand why in fact one lives nearly 30 years longer than the other.

It may help to visualize this problem of the determination of longevity to consider an illustrative analogy. Men behave in respect of their duration of life not unlike a lot of eight-day clocks cared for by an unsystematic person, who does not wind them all to an equal degree and is not careful about guarding them from accident. Some he winds up fully, and they run their full eight days.

Others he winds only halfway, and they stop after four days. Again the clock which has been wound up for the full eight days may fall off the shelf and be brought to a stop at the third day. Or someone may throw some sand in the works when the caretaker is off his guard. So, similarly, some men behave as though they had been wound up for a full 90-year run, while others are but partially wound up and stop at 40 or 65, or some other point. Or, again, the man wound up for 80 years may, like the clock, be brought up much short of that by an accidental invasion of microbes, playing the rôle of the sand in the works of the clock. It is of no avail for either the clock or the man to say that the elements of the mechanism are in whole or in major part capable of further service. The essential problem is: what determines the goodness of the original winding? And what relative part do external things play in bringing the running to an end before the time which the original winding was good for? It is with this problem of the winding up and running of the human mechanism that the present chapter will deal.

There are two general classes of factors which may be involved here. These are, on the one hand, heredity and, on the other hand, environment, using the latter term in the broadest sense. Inasmuch as we can be reasonably sure on *a priori* grounds that longevity, like most other biological phenomena, is influenced by both heredity and environment the problem practically reduces itself to the measuring of the relative importance of each of these two factor groups in determining the results we see. But before we start the discussion of exact measurements in this field let us first examine some of the general evi-

dence that heredity plays any part at all in the determination of longevity.

THE HYDE FAMILY

The first material which we shall discuss is that provided by the distinguished eugenist, Dr. Alexander Graham Bell, in his study of the Hyde family. Every genealogist is familiar with the "Genealogy of the Hyde Family," by Reuben H. Walworth. It is one of the finest examples in existence of careful and painstaking genealogical research. Upon the data included in this book, Bell has made a most interesting and penetrating analysis of the factors influencing longevity. At first thought one might conclude that highly biased results would probably flow from the consideration of only one family. Bell meets this point very well, however, in the following words:

> A little consideration will show that the descendants did not constitute a single family at all, and indeed had very little of the Hyde blood in them.
>
> Even the children of William Hyde owed only half of their blood to him, and one-half to his wife. The grandchildren owed only one-quarter of their blood to William Hyde, and three-quarters to other people, etc. The descendants of the seventh generation, and there are hundreds of them, owed only one sixty-fourth of their blood to William Hyde, and sixty-three sixty-fourths to the new blood introduced through successive generations of marriages with persons not of the Hyde blood at all.
>
> It will thus be seen that the thousands of descendants noted in the Hyde Genealogy constitute rather a sample of the general population of the country than a sample of a particular family in which family traits might be expected to make their appearance.

The substantial normality of the material is shown in Figure 41, which gives the l_x line, that is, the number of survivors at each age, of the 1,606 males and 1,352 females for whom data were available. The solid line is the male l_x line and the dotted line the female l_x. It is at once apparent that the curves have the same general

sweep in their passage over the span of life as has the general population life curve discussed in the preceding chapter. The descent is a little steeper in early adult life. The female curve differs in two respects from the normal general population curves. In the first place,

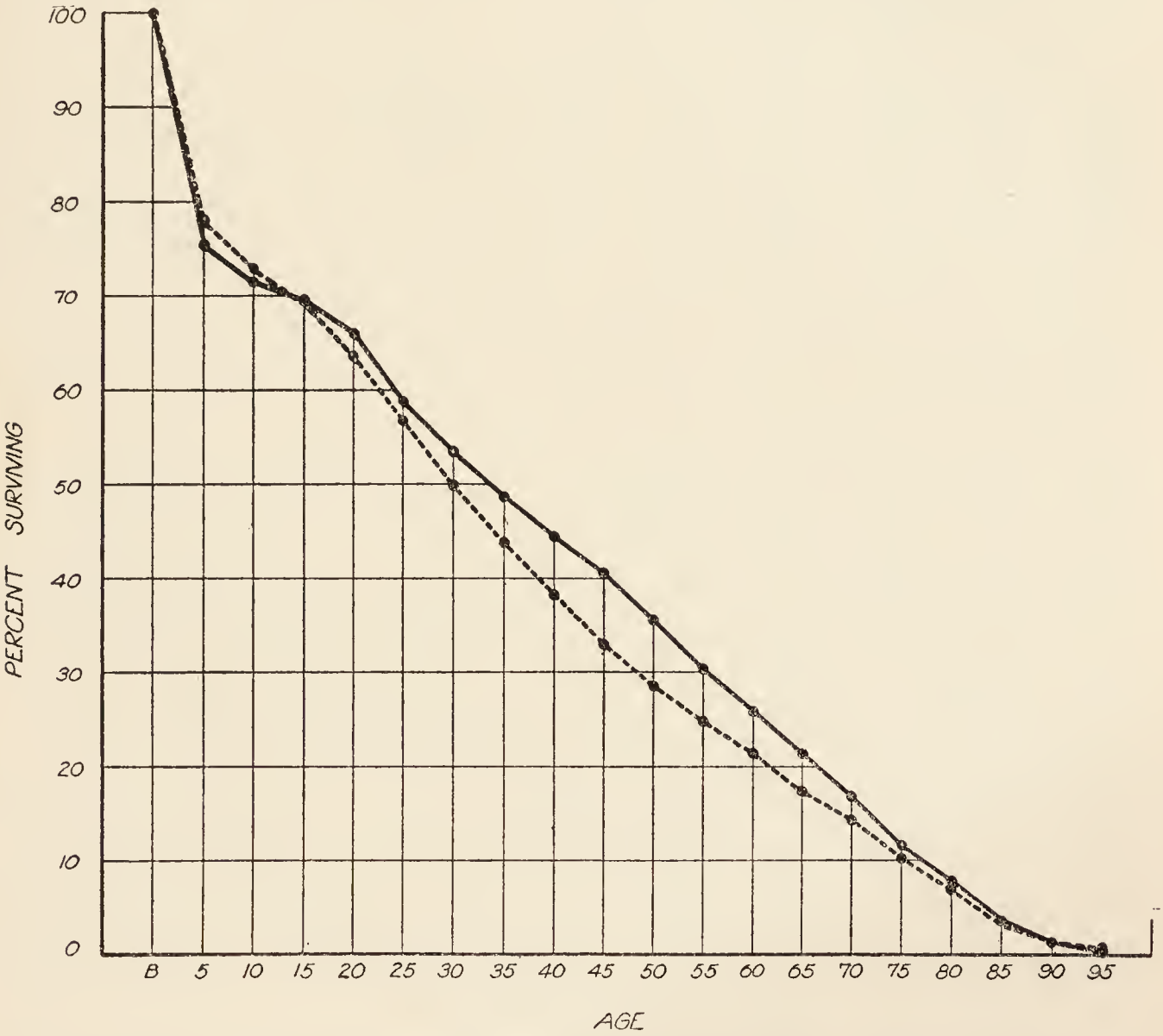


FIG. 41.—Showing survival curves of members of the Hyde family (Plotted from Bell's data).

beginning at age 15 and continuing to age 90, the female curve lies below that for the males, whereas normally for the general population it lies above it. This denotes a shorter average duration of life in the females than in the males, the actual figures being 35.8 years for the males and 33.4 years for the females. Bell attributes the difference to the strain of child-bearing by the females in

this rather highly fertile group of people, belonging in the main to a period when restrictions upon size of family were less common and less extensive than now. In the second place, the female l_x curve is actually convex to the base throughout a considerable portion of middle life whereas, normally, this portion of the curve presents a concave face to the base.

Apart from these deviations, which are of no particular significance for the use which Bell makes of the data, the Hyde material is essentially normal and similar to what one would expect to find in a random sample of the general population. In this material there were 2,287 cases in which the ages at death of the persons and the ages at death of their fathers were known. It occurred to Bell to arrange this material in such a way as to show what, if any, relation existed between age at death of the parent and that of the offspring. He arranged the parents into four groups, according to the age at which they died, and the offspring into five groups upon the same basis. In the case of the parents the groups were: First, those dying under 40; second, between 40 and 60; third, between 60 and 80; and fourth, at age 80 and over. The groups for the offspring were the same, except that the first was divided into two parts, namely, those dying under 20 and those dying between 20 and 40. The resulting figures are exhibited in Table 14.

The results for father and offspring are shown in Figure 42, based upon the data of Table 14. In each of the 5 polygons, one for each offspring group, the first dot shows the percentage of fathers dying under 40; the second dot the percentage of fathers dying between 40 and 60; and so on, the last dot in each curve showing the percentage of fathers dying at age 80 and over. It

TABLE 14

Analysis of the Hyde family data by person's age at death, showing the number and percentage having (a) fathers and (b) mothers who died at the age periods named. (From Bell)

Person's age at death	Father's age at death				
	Stated	-40	40-60	60-80	80+
Stated	2,287	66	522	1,056	643
Under 20	669	20	189	299	161
20 and under 40	538	18	140	269	111
40 and under 60	467	12	116	215	124
60 and under 80	428	13	57	196	162
80 and over	185	3	20	77	85
Percentages					
Stated	100.0	2.9	22.8	46.2	28.1
Under 20	100.0	3.0	28.2	44.7	24.1
20 and under 40	100.0	3.4	26.0	50.0	20.6
40 and under 60	100.0	2.6	24.8	46.0	26.6
60 and under 80	100.0	3.0	13.3	45.8	37.5
80 and over	100.0	1.6	10.8	41.6	46.0

Person's age at death	Mother's age at death				
	Stated	-40	40-60	60-80	80+
Stated	1,805	191	435	713	466
Under 20	511	88	129	199	95
20 and under 40	407	42	104	176	85
40 and under 60	379	27	92	159	101
60 and under 80	360	26	80	129	125
80 and over	148	8	30	50	60
Percentages					
Stated	100.0	10.6	24.1	39.5	25.8
Under 20	100.0	17.2	25.2	39.0	18.6
20 and under 40	100.0	10.3	25.6	43.2	20.9
40 and under 60	100.0	7.1	24.3	42.0	26.6
60 and under 80	100.0	7.2	22.2	35.9	34.7
80 and over	100.0	5.4	20.3	33.8	40.5

is to these last dots that attention should be particularly directed. It will be noted that the dotted line connecting the last dots of each of the 5 polygons in general rises as we pass from the left-hand side of the diagram to the right-hand side. In the case of offspring dying under 20, 24 per cent. of their fathers died at ages over 80. About

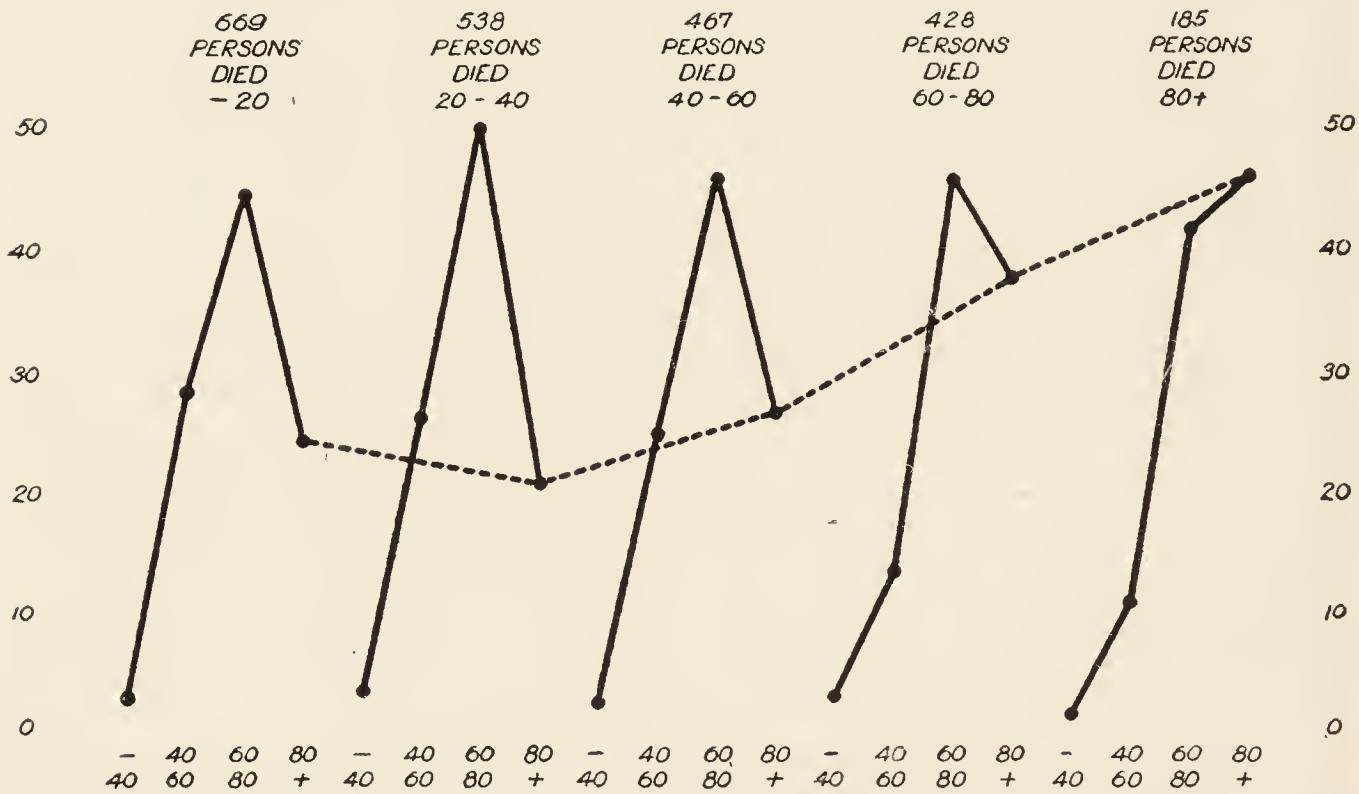


FIG. 42.—Influence of father's age at death upon longevity of offspring. First dot in each diagram shows the percentage having fathers who died at 40; second dot the percentage having fathers who died from 40-60; third dot the percentage having fathers who died from 60-80; fourth dot the percentage having fathers who died 80+ (After Bell).

21 per cent. of the fathers of offspring dying between 20 and 40 lived to be 80 years or over. For the next longer-lived group of offspring, dying between 40 and 60, the percentage of fathers living to 80 or over rose to 27 per cent. In the next higher group, the percentage is nearly 38, and finally the extremely long-lived group of offspring, the 185 persons who died at ages of 80 and over, had 46 per cent. or nearly one-half of their fathers living to the same great age. In other words, we see in general that the longer-lived a group of offspring is, on the average, the longer-lived are their fathers, on the average; or, put in another way, the higher the percentage of very

long-lived fathers which this group will have as compared with shorter-lived individuals.

Figure 43 shows the same sort of data for mothers and offspring. Here we see the curve of great longevity of parents rising in an even more marked manner than was the case with fathers of offspring. The group of

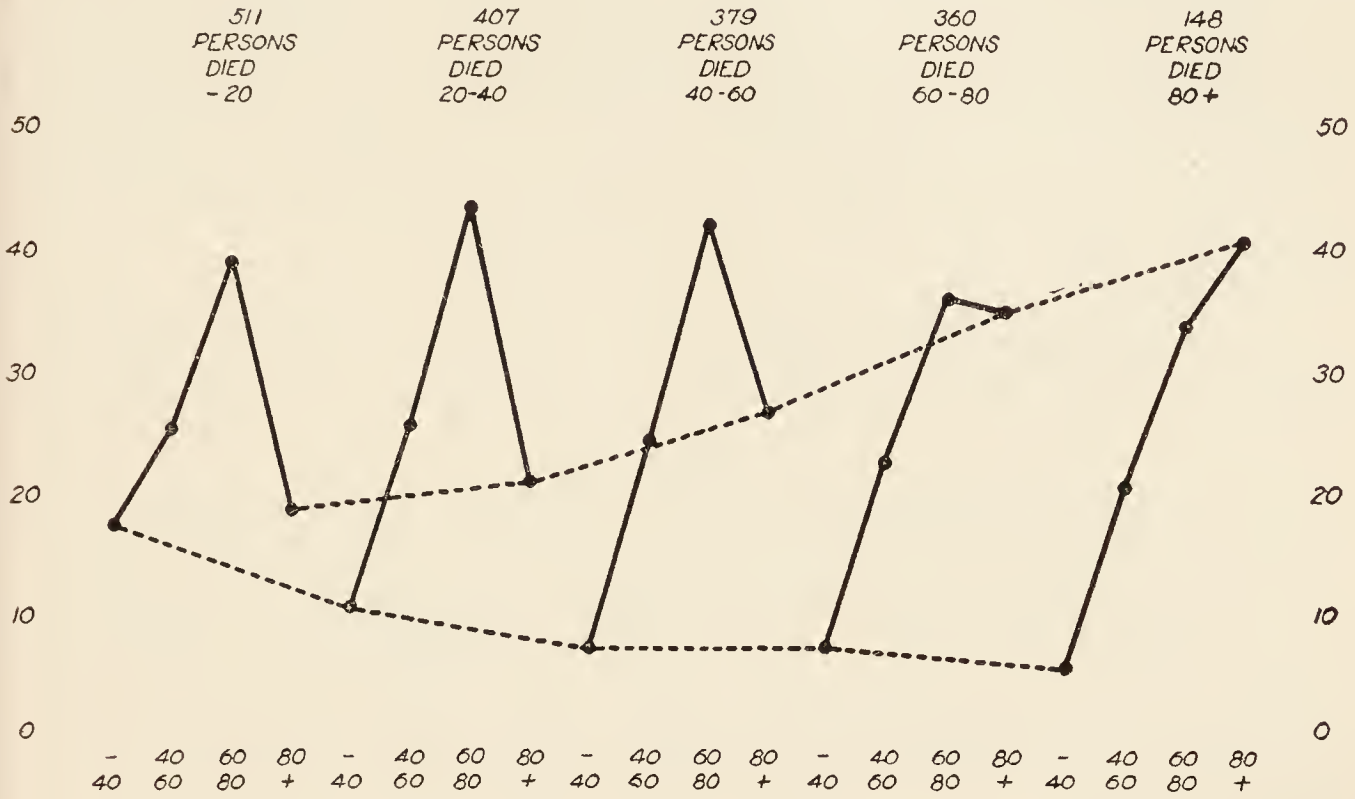


FIG. 43.—Influence of mother's age at death upon longevity of offspring. First dot in each diagram shows the percentage having mothers who died at 40; second dot the percentage having mothers who died at 40-60; third dot the percentage having mothers who died 60-80; fourth dot the percentage having mothers who died 80+ (After Bell).

offspring dying at ages under 20 had only 19 per cent. of their mothers living to 80 and over, whereas the group of offspring who lived to 80 and beyond had 41 per cent. of their mothers attaining the same great age. At the same time we note from the dotted line at the bottom of the chart that as the average age at death of the offspring increases, the percentage of mothers dying at early ages, namely, under 40, as given by the first dots, steadily *decreases* from 17 per cent. at the first group to just over 5 per cent. for the offspring dying at very advanced ages.

These striking results demonstrate at once that there is a definite and close connection between the average longevity of parents and that of their children. Extremely long-lived children have a much higher percentage of extremely long-lived parents than do shorter lived children. While the diagrams demonstrate the fact of this connection, they do not measure its intensity with as great precision as can be obtained by other methods of dealing with the data. A little farther on we shall take up the consideration of this more precise method of measurement of the hereditary influence in respect of longevity.

In the preceding diagrams we have considered each parent separately in connection with the offspring in

TABLE 15

Longevity of parents of persons dying at 80 and over. (From Bell)

Age at death of parents	Number of persons	Number of persons lived 80+	Per cent. of persons lived 80+
Stated	1,594	139	8.7
Lived to be 80+			
Neither parent	827	44	5.3
One parent (not other)	583	57	9.8
Both parents	184	38	20.6
Father (not mother)	337	38	11.3
Mother (not father)	246	19	7.7

regard to longevity. We shall, of course, get precisely the same kind of result if we consider both parents together. For the sake of simplicity, taking only the cases of extreme longevity, namely, persons living to 80 or over—the essential data are given in Table 15.

From this table it is seen that where neither parent lived to be 80, only 5.3 per cent. of the offspring lived to be 80 or over, the percentage being based upon 827

cases. Where one parent, but not the other, lived to be 80 or older, 9.8 per cent. of the offspring lived to be 80 or older, the percentage here being based upon 583 cases. Where both parents lived to be 80 or older 20.6 per cent. of the persons lived to the same great age, the percentage being based upon 184 cases. Thus it appears that in this group of people four times as many attained great longevity if both their parents lived to an advanced age, as attained this age when neither parent exhibited great longevity. The figures from the Hyde family seem further to indicate that the tendency of longevity is inherited more strongly through the father than through the mother. Where the father, but not the mother, lived to be 80 or older, 11.3 per cent. of the persons lived to age 80 or more, there being 337 cases of this kind. Where the mother, but not the father lived to be 80 or older, only 7.7 per cent., or nearly 4 per cent. fewer of the persons lived to the advanced age of 80 or more, there being 246 cases of this sort. Too much stress is not, however, to be laid upon this parental difference because the samples after all are quite small.

One other point in this table deserves consideration. Out of the 1,594 cases as a whole, less than 9 per cent. of the persons lived to the advanced age of 80 or more. But out of this number there are 767, or 48.1 per cent., nearly one-half of the whole, who had parents who lived to 80 or more years.

Another interesting and significant way in which one may see the great influence of the age of the parents at death upon the longevity of the offspring, is indicated in Table 16, where we have the average duration of life of individuals whose fathers and mothers died at the specified ages.

We see that the longest average duration of life, or expectation of life, was of that group which had both mothers and fathers living to age 80 and over. The average duration of life of these persons was 52.7 years. Contrast this with the average duration of life of those whose parents both died under 60 years of age, where

TABLE 16

Showing the influence of a considerable degree of longevity in both father and mother upon the expectation of life of the offspring. (After Bell). (In each cell of the table the open figure is the average duration of life of the offspring and the bracketed figure is the number of cases upon which the average is based).

Father's age at death	Mother's age at death		
	Under 60	60–80	Over 80
Under 60	32.8 years (128)	33.4 years (120)	36.3 years (74)
60–80	35.8 (251)	38.0 (328)	45.0 (172)
Over 80	42.3 (131)	45.5 (206)	52.7 (184)

the figure is 32.8 years. In other words, it added almost exactly 20 years to the average life of the first group of people to have extremely long-lived parents, instead of parents dying under age 60. In each column of the table the average duration of life advances as we proceed from top to bottom—that is, as the father's age at death increases—and in each row of the table the average expectation of life of the offspring increases as we pass from left to right—that is, with increasing age of the mother at death. However the matter is taken, a careful selection of one's parents in respect of longevity is the most reliable form of personal life insurance.

How great and deep is the significance of the facts shown in Table 16 may best be brought home to the mind by means of a comparison. Suppose this question to be asked: by how great an amount would the average expectation of life at birth (which in a stable population is the same thing as the mean duration of life) be increased if all the reasonably preventable deaths were prevented? If, say 75 per cent. of all the deaths from pulmonary tuberculosis did not occur; if 40 per cent. of the deaths from Bright's disease were prevented; and, in general, if all that medicine and hygiene knows today were put into reasonably effective operation, and nobody died except when and from such causes as could in no way be influenced by what medical science, good environment, etc., have to offer: by how much *then* would the expectation of life be greater than it now is? We have seen that to have one's parents live to 80 or over increases the expectation of life 20 years, as compared with that of persons whose parents die under 60 years of age. By how much more would the expectation of life be extended if all reasonably preventable deaths were prevented?

A thorough and critical answer to this question is afforded by an investigation of Forsyth's, conducted along the most exact and approved actuarial lines. Some years ago, Professor Irving Fisher sent a list of some 90 diseases to a group of the most prominent medical authorities in this country, and asked them to designate what percentage of the deaths due to each disease they considered preventable. The results of this inquiry were tabulated in an extremely conservative manner, with the result set forth in Table 16a, which is copied from Forsyth's paper (pp. 762-763).

TABLE 16a

Showing Fisher's ratios of preventability for the diseases enumerated in the mortality statistics of the United States, together with the relative importance of each disease as indicated by the percentage the number of its deaths bears to the total number of deaths

	Causes of death	Prominence of disease. Per cent. of all deaths	Ratio of preventability. Per cent.
1	Premature birth	2.0	40
2	Congenital malformation of the heart	.55	0
3	Other congenital malformations	.3	0
4	Congenital debility	2.3	40
5	Hydrocephalus	.1	0
6	Venereal diseases	.3	70
7	Diarrhœa and enteritis	7.74	60
8	Measles	.8	40
9	Acute bronchitis	1.1	30
10	Bronchopneumonia	2.4	50
11	Whooping cough	.9	40
12	Croup	.3	75
13	Meningitis	1.6	70
14	Diseases of larynx—not laryngitis	.07	40
15	Laryngitis	.06	40
16	Diphtheria	1.4	70
17	Scarlet fever	.5	50
18	Diseases of lymphatics	.01	20
19	Tonsillitis	.05	45
20	Tetanus	.19	80
21	Tuberculosis—not of lungs	.17	75
22	Abscess	.08	60
23	Appendicitis	.7	50
24	Typhoid fever	2.0	85
25	Puerperal convulsions	.2	30
26	Puerperal septicæmia	.4	85
27	Other diseases of childbirth	.36	50
28	Diseases of tubes	.1	65
29	Peritonitis	.5	55
30	Smallpox	.01	75
31	Tuberculosis of lungs	9.9	75
32	Violence	7.5	35
33	Malarial fever	.2	80
34	Septicæmia	.3	40
35	Epilepsy	.29	0
36	General, ill-defined, and unknown causes (including "heart failure," "dropsy," and "convulsions")	9.2	30
37	Erysipelas	.3	60
38	Pneumonia (lobar and unqualified)	7.0	45
39	Acute nephritis	.6	30
40	Pleurisy	.27	55
41	Acute yellow atrophy of liver	.02	0
42	Obstructions of intestines	.6	25

TABLE 16 a—Continued

	Causes of death	Prominence of disease. Per cent. of all deaths	Ratio of preventability. Per cent.
43	Alcoholism	.4	85
44	Hemorrhage of lungs	.1	80
45	Diseases of the thyroid body	.02	10
46	Ovarian tumor	.07	0
47	Uterine tumor	.1	60
48	Rheumatism	.5	10
49	Gangrene of lungs	.03	0
50	Anæmia, leukæmia	.4	50
51	Chronic poisonings	.05	70
52	Congestion of lungs	.4	50
53	Ulcer of stomach	.2	50
54	Carbuncle	.03	50
55	Pericarditis	.1	10
56	Cancer of female genital organs	.6	0
57	Dysentery	.5	80
58	Gastritis	.65	50
59	Cholera nostras	.09	50
60	Cirrhosis of liver	.9	60
61	General paralysis of insane	.3	75
62	Hyatid tumors of liver	.002	75
63	Endocarditis	.8	25
64	Locomotor ataxia	.17	35
65	Diseases of veins	.04	40
66	Cancer of breast	.4	0
67	Diabetes	.8	10
68	Biliary calculi	.17	40
69	Hernia	.27	70
70	Cancer not specified	.9	0
71	Tumor	.08	0
72	Bright's disease	5.6	40
73	Embolism and thrombosis	.26	0
74	Cancer of intestines	.55	0
75	Cancer of stomach and liver	1.7	0
76	Calculi of urinary tract	.03	10
77	Cancer of mouth	.1	0
78	Heart disease	8.1	25
79	Influenza	.7	50
80	Asthma and emphysema	.23	30
81	Angina pectoris	.4	25
82	Apoplexy	4.4	35
83	Cancer of skin	.2	0
84	Chronic bronchitis	.8	30
85	Paralysis	1.0	50
86	Softening of brain	.2	0
87	Diseases of arteries	.83	10
88	Diseases of bladder	.2	45
89	Gangrene	.25	60
90	Old age	2.0	0

It will be seen that these ratios of preventability are not all 100 per cent. They are not the wild overstatements of the propagandist. But they do represent, if they could be realized, substantial reductions from existing mortality rates.

TABLE 16b

Complete expectations of life as based upon the two assumptions that deaths are and are not prevented according to the ratios given in Table 16a

Age	Deaths		Loss in		Age	Deaths		Loss in	
	Not prevented	Prevented	Years	Days		Not prevented	Prevented	Years	Days
0	49.44	62.11	12	245	25	39.31	46.18	6	318
1	56.03	66.26	10	84	26	38.56	45.31	6	274
2	56.84	66.28	9	161	27	37.82	44.45	6	230
3	56.64	65.67	9	11	28	37.08	43.58	6	183
4	56.15	64.94	8	288	29	36.34	42.72	6	139
5	55.51	64.13	8	226	30	35.61	41.86	6	91
6	54.81	63.27	8	168	31	34.88	41.01	6	47
7	54.06	62.42	8	131	32	34.15	40.15	6	0
8	53.26	61.54	8	102	33	33.42	39.30	5	321
9	52.43	60.63	8	73	34	32.69	38.46	5	281
10	51.57	59.72	8	55	35	31.96	37.61	5	237
11	50.69	58.79	8	37	36	31.23	36.76	5	193
12	49.80	57.86	8	22	37	30.50	35.92	5	153
13	48.91	56.80	7	321	38	29.77	35.08	5	113
14	48.03	56.00	7	354	39	29.03	34.24	5	77
15	47.15	55.07	7	336	40	28.30	33.40	5	37
16	46.31	54.16	7	310	41	27.57	32.57	5	0
17	45.50	53.26	7	277	42	26.85	31.74	4	325
18	44.71	52.36	7	237	43	26.12	30.91	4	288
19	43.93	51.48	7	201	44	25.40	30.09	4	252
20	43.15	50.59	7	161	45	24.68	29.28	4	219
21	42.37	49.70	7	120	46	23.97	28.47	4	183
22	41.60	48.82	7	80	47	23.26	27.67	4	150
23	40.83	47.94	7	40	48	22.56	26.87	4	113
24	40.07	47.06	6	261	49	21.87	26.09	4	80

On the basis of the mortality experience of the Registration Area for 11 years (1900-1910) Forsyth calculated mortality tables on the assumption that the ratios of preventability of Table 16a were actually in full operation. The results, so far as concerns expectation of life, are set forth in Table 16b.

From the first line of this table it is perceived that the total increase in expectation of life which would result if Fisher's ratios of preventability were fully realized *is just under 13 years!* How unfavorably this contrasts with the 20 years increase shown by the two

TABLE 16b—Continued

Age	Deaths		Loss in		Age	Deaths		Loss in	
	Not prevented	Prevented	Years	Days		Not prevented	Prevented	Years	Days
50.....	21.17	25.30	4	47	71.....	8.82	11.15	2	120
51.....	20.47	24.52	4	18	72.....	8.36	10.59	2	84
52.....	19.78	23.74	3	350	73.....	7.93	10.04	2	40
53.....	19.09	22.97	3	321	74.....	7.50	9.51	2	4
54.....	18.40	[22.21	3	296	75.....	7.09	8.99	1	329
55.....	17.74	[21.46]	3	263	76.....	6.70	8.49	1	288
56.....	17.08	20.72	3	234	77.....	6.31	8.00	1	252
57.....	16.45	20.00	3	201	78.....	5.98	7.53	1	201
58.....	15.83	19.30	3	193	79.....	5.64	7.07	1	157
59.....	15.23	18.61	3	139	80.....	5.32	6.63	1	113
60.....	14.63	17.93	3	110	81.....	5.02	6.20	1	66
61.....	14.05	17.27	3	80	82.....	4.74	5.78	1	15
62.....	13.48	16.61	3	47	83.....	4.47	5.38		332
63.....	12.92	15.96	3	15	84.....	4.23	4.99		277
64.....	12.36	15.32	2	350	85.....	4.01	4.62		223
65.....	11.82	14.69	2	348	86.....	3.79	4.25		168
66.....	11.29	14.07	2	285	87.....	3.58	3.89		113
67.....	10.77	13.47	2	256	88.....	3.39	3.56		62
68.....	10.26	12.87	2	223	89.....	3.22	3.27		18
69.....	9.77	12.29	2	190	90.....	3.06	3.06		0
70.....	9.29	11.71	2	153					

corner diagonal cells of Table 16! No more striking demonstration could be found of the overwhelming importance of heredity in determining duration of life. For if all the deaths which reason will justify one in supposing preventable on the basis of what is now known, were prevented in fact *the resulting increase in expectation of life falls seven years short of what might reasonably be expected to follow the selection of only one generation of ancestry (the parental) for longevity.*

So much for Bell's analysis of longevity in the Hyde

family. We have seen that it demonstrates with the utmost clearness and certainty that there is an hereditary influence between parent and offspring affecting the expectation of longevity of the latter. Bell's method of handling the material does not provide any precise measure of the intensity of this hereditary influence, nor does it furnish any indication of its strength in any but the direct line of descent. Of course, if heredity is a factor in the determination of longevity we should expect its effects to be manifested as between brothers and sisters, or in the avuncular relationships, and in greater or less degree in all the other collateral and more remote direct degrees of kinship. Happily, we have a painstaking analysis, with a quantitative measure of the relative influence of heredity in the determination of longevity, which was carried out many years before Bell's work on the Hyde family, by the pioneer in this field, Prof. Karl Pearson. His demonstration of the inheritance of longevity appeared more than twenty years before that of Bell. I have called attention to the latter's work first merely because of the greater simplicity and directness of his demonstration. We may now turn to a consideration of Pearson's more detailed results.

PEARSON'S WORK

The material used by Pearson and his student, Miss Beeton, who worked with him on the problem, came from a number of different sources. Their first study dealt with three series from which all deaths recorded as due to accident were excluded. The first series included one thousand cases of the ages of fathers and sons at death, the latter being over 22.5 years of age, taken

from Foster's "Peerage." The second series consisted of a thousand pairs of fathers and sons, the latter dying beyond the age of 20, taken from Burke's "Landed Gentry." The third series consisted of ages at death of one thousand pairs of brothers dying beyond the age of 20 taken from the "Peerage." It will be noted that all these series considered in this first study dealt only with inheritance in the male line. The reason for this was simply that in such books of record as the "Peerage" and "Landed Gentry" sufficiently exact account is not given of the deaths of female relatives. In a second study the material was taken from the pedigree records of members of the English Society of Friends and from the Friends' Provident Association. This material included data on inheritance of longevity in the female line and also provided data for deaths of infants, which were lacking in the earlier used material. The investigation was grounded upon that important branch of modern statistical calculus known as the method of correlation. For each pair of relatives between whom it was desired to study the intensity of inheritance of longevity a table of double entry was formed, like the one shown here as Table 17.

The figures in each cell or compartment of this table denote the frequency of occurrence of pairs of fathers and adult sons having respectively the durations of life indicated by the figures in the margins. Thus we see, examining the first line of the table, that there were 11 cases in which the average duration of life of the father was 48 years and that of the adult son 23 years. Farther down and to the right in the table there were 13 cases in which the average duration of life of the father and the son was in each case 83 years. These cases are men-

tioned merely as illustrations. The whole table is to be read in the same manner.

From such a table as this it is possible to calculate, by well-known mathematical methods, a single numerical constant of somewhat unique properties known as the

TABLE 17

Correlation table showing the correlation between father and son in respect of duration of life

DURATION OF LIFE OF SON	DURATION OF LIFE OF FATHER																	
	23	28	33	38	43	48	53	58	63	68	73	78	83	88	93	98	103	Totals
23	1	1	2	5	3	11	6	7	11	9	6	12	8	2		2		86
28				1	6	4	5	12	15	10	13	10	7		1	1		85
33			1	2	2	5	7	8	7	10	7	8	8	4	1			70
38		1	1	2		2	8	5	3	9	11	11	9	5	2	1		70
43		1			1	5	1	5	6	11	10	10	17	5				72
48			1	1	2	5	5	4	6	9	12	15	5	3				68
53		1		3		5	7	3	2	11	11	14	10	1	1	1		70
58			1	3		4	5	10	8	10	5	8	9	3		2		68
63		2	1	3	5	1	4	8	13	9	11	11	11	5				84
68			1	6	3	6	7	5	5	6	14	16	12	7	2			90
73		1		2	1	6	5	4	7	9	10	14	13	8	8	1	1	90
78			1	1	2	2	4	4	4	10	5	8	9	4		3		57
83				1	1	5	3	1	2	3	7	10	13	3	2	2		53
88		1				2	3		1	4	7	5	1	2		2		28
93						1				2	2							5
98						1						1		1	1			4
Totals	1	8	9	30	26	65	70	76	90	122	131	153	132	53	18	15	1	1000

coefficient of correlation, which measures the degree of association or mutual dependence of the two variables included in such double entry tables. This coefficient measures the amount of resemblance or association between characteristics of individuals or things. It is stated in the form of a decimal which may take any value between 0 and 1. As the correlation coefficient rises to 1 we approach a condition of absolute dependence of the variables one upon the other. As it falls to zero we approach a condition of absolute independence, where the one variable has no relation to the other in the amount

or direction of its variation. The significance of a correlation coefficient is always to be judged, in any particular case, by the magnitude of a constant associated with it called the probable error. A correlation coefficient may be regarded as certainly significant when it has a value of 4 or more times that of its probable error, which is always stated after the coefficient with a combined plus and minus sign between the two. The coefficient is probably significant when it has a value of not less than 3 times its probable error. By "significant" in this connection is meant that the coefficient probably is not merely a random chance result.

In Table 18 are the numerical results from the first study based upon the "Peerage" and "Landed Gentry."

TABLE 18

Inheritance of duration of life in male line. Data from "Peerage" and "Landed Gentry." (Beeton and Pearson).

Relatives		Correlation coefficient	Ratio of coefficient to its probable error
x	y	r_{xy}	$r_{xy} \div E_r$
Father ("Peerage")	Son, 25 years and over	$.115 \pm .021$	5.5
Father ("Landed Gentry")	Son, 20 years and over	$.142 \pm .021$	6.8
Father ("Peerage")	Son, 52.5 years and over	$.116 \pm .023$	5.0
Father ("Landed Gentry")	Son, 50 years and over	$.113 \pm .024$	4.7
Brother ("Peerage")	Brother	$.260 \pm .020$	13.0

It is seen at once that all of the coefficients are significant in comparison with their probable errors. The last column of the table gives the ratio of the coefficient to its probable error, and in the worst case the coefficient is 4.7 times its probable error. The odds against such a correlation having arisen from chance alone are about 655 to 1. Odds such as these may be certainly taken as demonstrating that the results rep-

resent true organic relationship and not mere chance. All of the other coefficients are certainly significant, having regard to their probable errors. Furthermore, they are all positive in sign, which implies that a variation in the direction of increased duration of life in one relative of the pair is associated with an increase in expectation of life in the other. It will be noted that the magnitude of the correlation between brother and brother is about twice as great as in the case of correlation of father with son. From this it is provisionally concluded that the intensity of the hereditary influence in respect of duration of life is greater in the fraternal relationship than in the parental. It evidently makes no difference, broadly speaking, so far as these two sets of material are concerned, whether there are included in the correlation table all adult sons, whatever their age, or only adult sons over 50 years of age. The coefficients in both cases are essentially of the same order of magnitude.

Perhaps someone will be inclined to believe that the correlation between father and son, and brother and brother, in respect of the duration of life arises as a result of similarity of the environments to which they are exposed. Pearson's comments on this point are penetrating, and I believe absolutely sound. He says:

> There may be some readers who will be inclined to consider that much of the correlation of duration of life between brothers is due to there being a likeness of their environment, and that thus each pair of brethren is linked together and differentiated from the general population. But it is difficult to believe that this really affects *adult* brothers or a father and his adult offspring. A man who dies between 40 and 80 can hardly be said to have an environment more like that of his brother or father, who died also at some such age, than like any other member of the general population. Of course, two brothers have usually a like environment in infancy, and their ages at death, even if they die adults, may be influenced by their rearing. But if this be true, we ought to find a high correlation in ages

at death of brethren who die as minors. As a matter of fact this correlation for minor and minor is 40 to 50 per cent. less than in the case of adult and adult. It would thus seem that identity of environment is not the principal factor in the correlation between ages of death, for this correlation is far less in youth than in old age.

TABLE 19

Inheritance of duration of life. Data from Quaker records.
(Beeton and Pearson)

Relatives		Correlation coefficient	Ratio of coefficient to its probable error
x	y	r_{xy}	$r_{xy} \div E_r$
Father	Adult son	0.135 ± .021	6.4
Father	Minor son	.087 ± .022	4.0
Father	Adult daughter	.130 ± .020	6.5
Father	Minor daughter	.052 ± .023	2.3
Mother	Adult son	.131 ± .019	6.9
Mother	Minor son	.076 ± .024	3.2
Mother	Adult daughter	.149 ± .020	7.5
Mother	Minor daughter	.138 ± .024	5.7
Elder adult brother	Younger adult brother	.229 ± .019	12.1
Adult brother	Adult brother	.285 ± .020	14.3
Minor brother	Minor brother	.103 ± .029	3.6
Adult brother	Minor brother	−.026 ± .025	1.0
Elder adult sister	Younger adult sister	.346 ± .018	19.2
Adult sister	Adult sister	.332 ± .019	17.5
Minor sister	Minor sister	.175 ± .031	5.6
Adult sister	Minor sister	−.026 ± .029	.9
Adult brother	Adult sister	.232 ± .015	15.5
Minor brother	Minor sister	.144 ± .025	5.8
Adult brother	Minor sister	−.006 ± .035	.2
Adult sister	Minor brother	−.027 ± .024	1.1

The cases above the horizontal line are all direct lineal inheritance; those below the line collateral inheritance.

The results regarding minors to which Pearson refers are shown in Table 19. This table gives the results of the second study made by Beeton and Pearson on inheritance of duration of life, based upon the records of the

Friends' Societies. It appears in the upper half of the table that wherever a parent, father or mother, appears with a minor son or daughter the correlation coefficients are small in magnitude. In some cases they are just barely significant in comparison with their probable errors as for example, the correlation of father and minor son, and that of mother and minor daughter. In the other cases involving minors the coefficients are so small as to be insignificant. On the other hand, in every case of correlation between parent and *adult* offspring of either sex, the coefficient is 6 or more times its probable error, and must certainly be regarded as significant. It will further be noted that the magnitude of the coefficients obtained from these Quaker records is of the same general order as was seen in the previous table based on the "Peerage" and "Landed Gentry" material.

The lower part of the table gives the results for various fraternal relationships. In general the fraternal correlations are higher that the parental. The coefficients for minors or for minors with adults are very low and in most cases not significantly different from zero. In four cases—namely, adult brother with minor brother; adult sister with minor sister; adult brother with minor sister; and adult sister with minor brother—the coefficients are all negative in sign, although in no one of the cases is the coefficient significant in comparison with its probable error. A minus sign before a correlation coefficient means that an increase in the value of one of the variables is associated with a decrease in the value of the other. So that these negative coefficients would mean, if they were significant, that the greater the age at death of an adult brother, the lower the age at death of his minor brother or sister. But the coefficients are actually sensibly equal to zero. Pearson

points out that the minus sign in the case of these correlations of adult with minor exhibits the effect of the inheritance of the mortality of youth. Minors dying from 16 to 20 are associated with adults dying from 21 to 25. That is, minors dying late correspond to adults dying early. This situation may be a peculiarity of the Quaker material with which this work deals. There is urgent need for further study of the inheritance of the duration of life on more and better material than any which has hitherto been used for the purpose. I have under way in my own laboratory at the present time an extensive investigation of this kind, in which there will be hundreds of thousands of pairs of relatives in the individual correlation tables instead of thousands, and all types of collateral kinship will be represented. Because of the magnitude of the investigation, however, it will be still a number of years before the results will be in hand for discussion.

The facts which have been presented leave no doubt as to the reality of the inheritance factor as a prime determinant of the length of the life span.

At the beginning it was pointed out that it was on *a priori* grounds highly probable that duration of life is influenced by both heredity and environment, and that the real problem is to measure the comparative effect of these two general sets of factors. We have seen that the intensity of inheritance of duration of life, taking averages, is of the order indicated by the following coefficients.

Parental correlation (adult children) $r = .1365$
Fraternal correlation (adults) $r = .2831$

Now we have to ask this question: What are the values of parental and fraternal correlation for characters but slightly if at all affected in their values by the environment? Happily, Pearson has provided such values in his

extensive investigations on the inheritance of physical characters in man.

In Table 20 are given the values of the parental correlations for the four physical characters—stature, span, forearm length, and eye color. Now it is obvious

TABLE 20

Parental inheritance of physical characters in man. (Pearson)

Pair	Organ	Correlation
Father and Son	Stature	.51
Father and Son	Span	.45
Father and Son	Forearm	.42
Father and Son	Eye color	.55
Father and Daughter	Stature	.51
Father and Daughter	Span	.45
Father and Daughter	Forearm	.42
Father and Daughter	Eye color	.44
Mother and Son	Stature	.49
Mother and Son	Span	.46
Mother and Son	Forearm	.41
Mother and Son	Eye color	.48
Mother and Daughter	Stature	.51
Mother and Daughter	Span	.45
Mother and Daughter	Forearm	.42
Mother and Daughter	Eye color	.51

that the differences of environmental forces impinging upon the various members of a homogeneous group of middle class English families (from which source the data for these correlations were drawn) can by no possibility be great enough to affect sensibly the stature, the arm-length, or the eye color of the adults of such families. It would be preposterous to assert that the resemblance between parents and offspring in respect of eye color is due solely, or even sensibly, to similarity of environment.

It is due to heredity and substantially nothing else. Now the average value of the 16 parental coefficients for the inheritance of physical characters shown in the table is

$$r = .4675$$

Table 21 shows the coefficients for the fraternal inheritance of six physical characters, cephalic index (the ratio of head length and head breadth) and hair color having been added to those given in the parental table. Again it is seen that the coefficients have all about the

TABLE 21

Fraternal inheritance of physical characters in man. (Pearson)

Pair	Organ	Correlation
Brother and Brother	Stature	.51
Brother and Brother	Span	.55
Brother and Brother	Forearm	.49
Brother and Brother	Eye color	.52
Brother and Brother	Cephalic index	.49
Brother and Brother	Hair color	.59
Sister and Sister	Stature	.54
Sister and Sister	Span	.56
Sister and Sister	Forearm	.51
Sister and Sister	Eye color	.45
Sister and Sister	Cephalic index	.54
Sister and Sister	Hair color	.56
Brother and Sister	Stature	.55
Brother and Sister	Span	.53
Brother and Sister	Forearm	.44
Brother and Sister	Eye color	.46
Brother and Sister	Cephalic index	.43
Brother and Sister	Hair color	.56

same values, and it is as apparent as before that the resemblance between brother and sister, for example, in eye-color, or arm length, or shape of head cannot for a moment, because of the nature of the characters themselves, be supposed to have arisen because of the similarity of environment. The average value of all these fraternal coefficients is

$$r = .5156$$

From these data, with the help of a method due to Pearson, it is possible to determine the percentage of the

death rate dependent upon the inherited constitution, and the percentage not so dependent. If pN be the number of deaths in N cases which depend in no way upon the inherited constitution of the individual, then $(1\text{-}p)$ will represent the chance of an individual dying because of his inherited constitutional makeup, and $(1\text{-}p)^2$ will be the chance of a pair of individuals, say two brothers, both dying from causes determined by inheritance. If further r denotes the observed correlation between individuals in respect of duration of life, and r_0 the correlation between the same kin in respect of such measured physical characters as those just discussed, in the determination of which it is agreed that environment can play only a small part, we have the following relation:

$$\frac{r}{r_0} = (1\text{-}p)^2$$

Substituting the ascertained values we have

1. From parental correlations.

$$0.1365 = .4675\ (1\text{-}p)^2$$
$$(1\text{-}p)^2 = .292$$
$$(1\text{-}p) = .54$$

2. From fraternal correlations

$$0.2831 = .5156\ (1\text{-}p)^2$$
$$(1\text{-}p) = .74$$

From these figures it may be concluded, and Pearson does so conclude, that from 50 to 75 per cent. of the general death rate within the group of the population on which the calculations are based, is determined fundamentally by factors of heredity and is not capable of essential modification or amelioration by any sort of environmental action, however well intentioned, however costly, or however well advertised. *Mutatis mutandis* the same conclusion applies to the duration of life. I have

preferred to state the conclusion in terms of death rates, as it was originally stated by Pearson, because of the bearing it has upon a great deal of the public health propaganda so loosely flung about. It need only be remembered that there is a perfectly definite functional relation between death rate and average duration of life in an approximately stable population group, expressible by an equation, in order to see that any conclusion as to the relative influence of heredity and environment upon the general death rate must apply with equal force to the duration of life.

THE SELECTIVE DEATH RATE IN MAN

If the duration of life were inherited it would logically be expected that some portion of the death rate must be selective in character. For inheritance of duration of life can only mean that when a person dies is in part determined by that individual's biological constitution or makeup. And equally it is obvious that individuals of weak and unsound constitution must, on the average, die earlier than those of strong, sound, and vigorous constitution. Whence it follows that the chances of leaving offspring will be greater for those of sound constitution than for the weaklings. The mathematical discussion which has just been given indicates that from one-half to three-fourths of the death rate is selective in character, because that proportion is determined by hereditary factors. Just in proportion as heredity determines the death rate, so is the mortality selective. The reality of the fact of a selective death rate in man can be easily shown graphically.

In Figure 44 are seen the graphs of some data from European royal families, where no neglect of children,

degrading environmental conditions, or economic want can have influenced the results. These data were com-

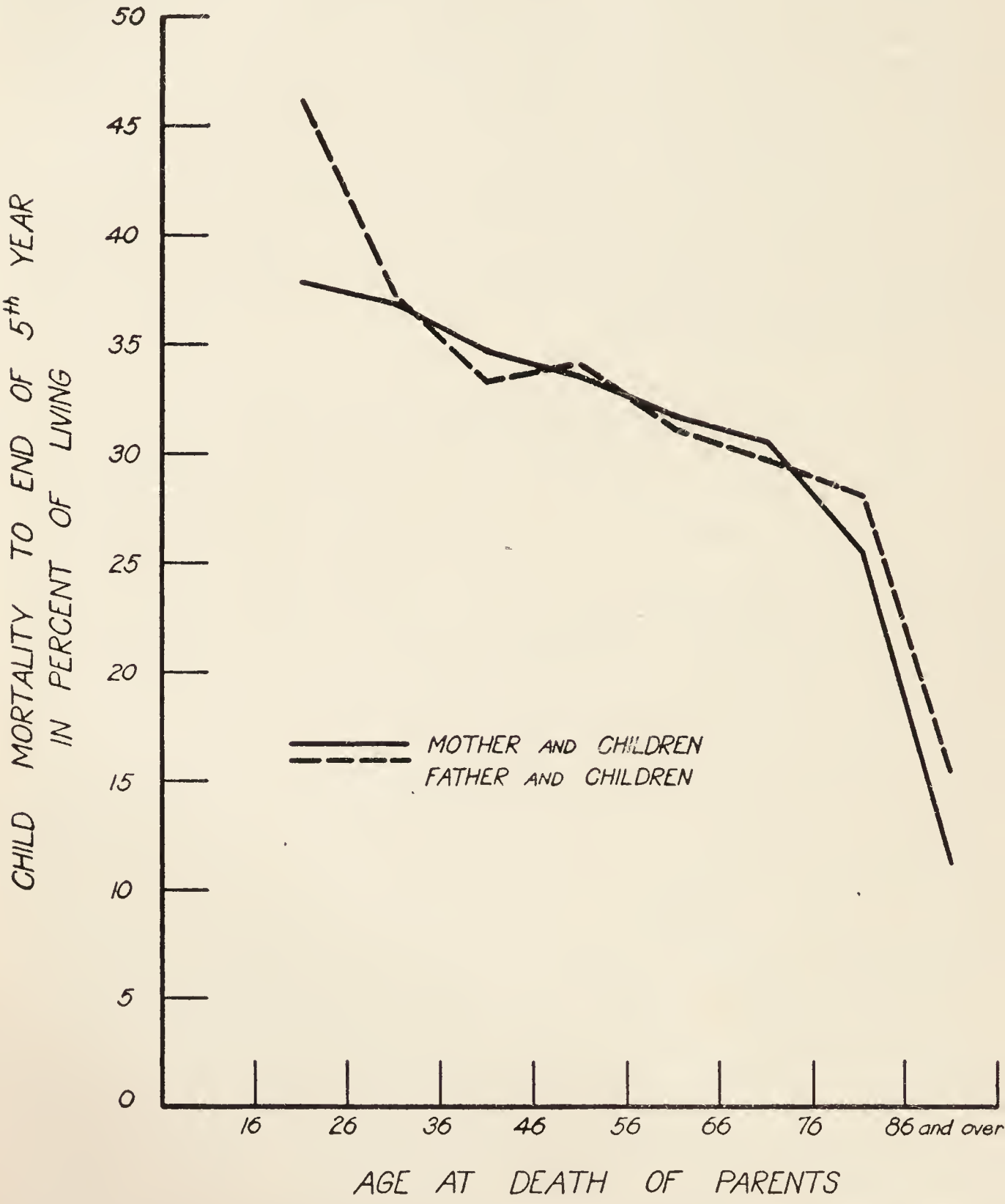


FIG. 44.—Diagram showing the influence of age at death of parents upon the percentage of offspring dying under 5 years. (After Ploetz).

piled by the well-known German eugenist, Professor Ploetz of Munich. The lines show the falling per-

centage of the infantile death rate as the duration of life of the father and mother increases. Among the children of short-lived fathers and mothers, at the left end of each line, is found the highest infant mortality, while among the offspring of long-lived parents the lowest infant mortality occurs, as shown at the right-hand end of the diagram.

The results so far presented regarding a selective death rate and inheritance of duration of life, have come from selected classes: the aristocracy, royalty or Quakers. None of these classes can be fairly said to represent the general population. Can the conclusion be transferred safely from the classes to the masses? To the determination of this point one of Pearson's students, Dr. E. C. Snow, addressed himself. The method which he used was, from the necessities of the case, a much more complicated and indirect one than that of Pearson and Ploetz. Its essential idea was to see whether infant deaths weeded out the unfit and left as survivors the stronger and more resistant. All the infants born in a single year were taken as a cohort and the deaths occurring in this cohort in successive years were followed through. Resort was had to the method of partial or net correlation. The variables correlated in the case of the Prussian data were these:

1. x_0 = Births in year a given cohort started.
2. x_1 = Deaths in the first two years of life.
3. x_2 = Deaths in the next eight years of life.
4. x_3 = Deaths in the ten years of all individuals not included in the particular cohort whose deaths are being followed.

In the case of the English data the variables were:

x_0 = Births in specified year.
x_1 = Deaths in the first three years of life of those born in specified year.
x_2 = Deaths in fourth and fifth years of life of those born in specified year.
x_3 = The "remaining" deaths under 5.

The underlying idea was to get the partial or net correlation between x_1 and x_2, while x_0 and x_3 are held constant. If the mortality of infancy is selective, its amount should be negatively correlated to a significant degree with the mortality of the next eight years when the births in each district considered are made constant and when the general health environment is made constant. Under the constant conditions specified a negative correlation denotes that the heavier the infan-

TABLE 22

Snow's results on selective death rate in man. English and Prussian rural districts

Data			Actual correlation $r_{12.03}$	Expected correlation if no selection
Males:				
	English Rural Districts	(1870)	−0.4483	−0.0828
		(1871)	− .3574	− .1014
		(1872)	− .2271	− .0807
	Prussian Rural Districts	(1881)	− .9278	− .0958
		(1882)	− .6050	− .0765
Females:				
	English Rural Districts	(1870)	− .4666	− .0708
		(1871)	− .2857	− .0505
		(1872)	− .5089	− .0496
	Prussian Rural Districts	(1881)	− .8483	− .0933
		(1882)	− .6078	− .0705

tile death rate in a cohort of births the lighter will be the death rate of later years, and *vice versa.* The last variable, x_3, is the one chosen, after careful consideration and many trials, to measure variation in the health environment. If any year is a particularly unhealthy one—an epidemic year for example—then this unhealthiness should be accurately reflected in the deaths of those members of the population not included in the cohort under review.

Snow's results for English and Prussian rural districts are set forth in Table 22. From this table it is seen that in every case the correlations are *negative*, and therefore indicate that the mortality of early life is selective. Furthermore, the demonstration of this fact is completed by showing that the observed coefficients are from 3 to 10 times as great as they would be if there were no selective character to the death rate. The coefficients for the Prussian population, it will be noted, are of a distinctly higher order of magnitude than those for the English population. This divergence is probably due chiefly to differences in the quality of the fundamental statistical material in the two cases. The Prussian material is free from certain defects inherent in the English data, which cannot be entirely got rid of. The difference in the coefficients for the two successive Prussian cohorts represents, in Snow's opinion, probably a real fluctuation in the intensity of natural selection in the one group as compared with the other. How significant Snow's results are is shown graphically in Figure 45.

Snow's own comments on his results are significant. He says:

> The investigations of this memoir have been long and laborious, and the difficulties presented by the data have been great. Still, the general result cannot be questioned. *Natural selection, in the form of a selective death-rate, is strongly operative in man in the early years of life.* Those data which we believe to be the best among those we have used—the Prussian figures—show very high negative correlation between the deaths in the first two years of life and those in the next eight, when allowance is made for difference in environment. We assert with great confidence that a high mortality in infancy (the first two years of life) is followed by a corresponding low mortality in childhood, and conversely. The English figures do not allow such a comprehensive survey to be undertaken, but, so far as they go, they point in the same direction as the Prussian ones. The migratory tendencies in urban districts militate against the detection of selective influences there, but we express the belief that those influences

are just as prevalent in industrial as in rural communities, and could be measured by other means if the data were forthcoming.

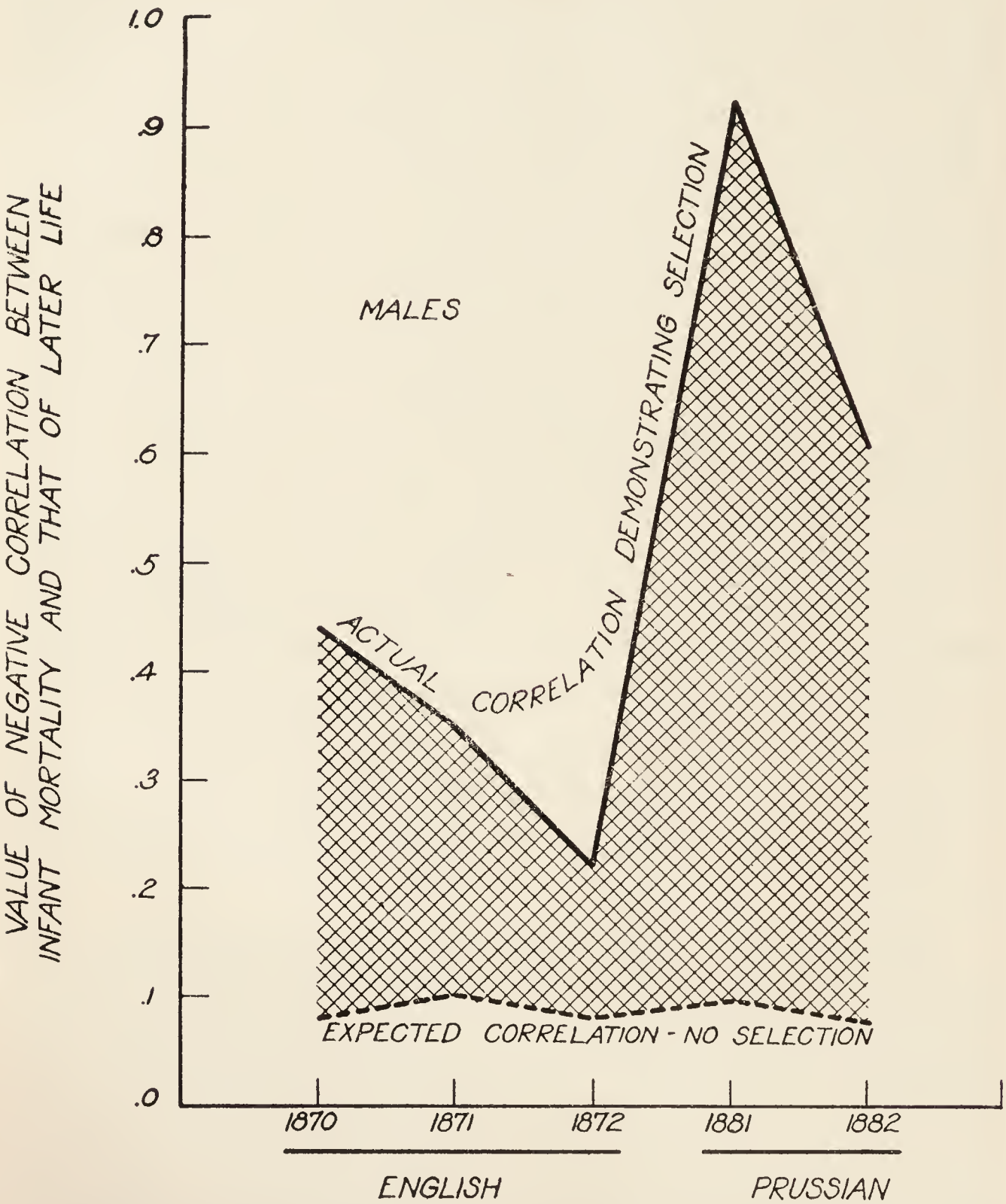


Fig. 45.—Snow's results on selective death rate in man. The cross-hatched area may be taken, in comparison with the small clear area at the bottom, as indicating the influence of the selective death rate in increasing the correlations.

Our investigation substantiates for a general population the results found by Pearson and Ploetz for more restricted populations, and disagrees with many statements of health officers. It is with great reluctance that

we point out this disagreement, and assert a doctrine which, in the present sentiment of society, is bound to be unpopular. We have no feelings of antagonism towards the efforts which have been made in recent years to save infant life, but we think that the probable consequences of such actions, so far as past experience can indicate them, should be completely understood. All attempts at the reduction of mortality of infancy and childhood should be made in the full knowledge of the facts of heredity. Everybody knows the extreme differences in constitutional fitness which exist in men and women. Few intelligent people can be ignorant of the fact that this constitutional fitness is inherited according to laws which are fairly definitely known. At the same time marriage is just as prevalent among those of weak stocks as among those of the vigorous, while the fertility of the former is certainly not less than that of the latter. Thus a proportion of the infants born every year must inevitably belong to the class referred to in the report as "weaklings," and, with Pearson's results before us, we are quite convinced that true infantile mortality (as distinct from the mortality due to accident, neglect, etc.—no small proportion of the whole) finds most victims from among this class. Incidentally we would here suggest that no investigation into the causes of infant and child mortality is complete until particulars are gathered by the medical officers of the constitutional tendencies and physical characters of the parents.

Our work has led us to the conclusion that infant mortality *does* effect a "weeding out" of the unfit; but, though we would give this conclusion all due emphasis, we do not wish to assert that any effort, however small, to the end of reducing this mortality is undesirable. Nobody would suggest that the difference between the infant rates in Oxfordshire and Glamorganshire (73 and 154 per 1,000 births respectively, in 1908) was wholly due to the constitutional superiority of the inhabitants of the former county. The "weeding-out" process is not uniform. In the mining districts of South Wales, accident, negligence, ignorance and insanitary surroundings account for much. By causing improvements under these heads it may be possible to reduce the infant mortality of Glamorganshire by the survival of many who are not more unfit than are those who survive in Oxfordshire, and the social instincts of the community insist that this should be done.

This work of Snow's aroused great interest, and soon after it appearance was controverted, as it seems to me quite unsuccessfully, by Brownlee, Saleeby and others.

Happily the results of Pearson, Ploetz and Snow on the selective death rate have recently been accorded a confirmation and extension to still another group of

people—the Dutch—in some investigations carried out by Dr. F. S. Crum of the Prudential Life Insurance Company, with the assistance of the distinguished mathematical statistician, Mr. Arne Fisher.

The Dutch Government publishes annually data which undoubtedly furnish the best available material now existing in the world for the purpose of determining whether or not there is a positive or negative correlation between infant mortality and the mortality in the immediately subsequent years of life. Fisher's mathematical analysis embraces a very large body of material, including nearly a million and a half births, and nearly a quarter of a million deaths of males occurring in the first five years of life. The Holland data make it possible to develop life tables for every cohort of births and this has been done in the 16 cohorts of males during the years 1901-1916. The data also make it possible to work up these life tables for urban areas and for rural areas. After carefully eliminating secular disturbances the Holland material appears to prove quite conclusively for the rural districts that there is a definite negative correlation, of significant magnitude, between infant mortality and the mortality in the immediately subsequent years of life. The only place where positive correlation appears is in the four large cities of the country with more than a hundred thousand inhabitants each. Fisher makes the following point (in a letter to the present writer) in explanation of these positive correlations. He says:

> The larger cities are better equipped with hospital and clinical facilities than the smaller cities and the rural districts. More money is also spent on child welfare. Is it therefore not possible that many feeble lives who in the course of natural circumstances would have died in the first year of life are carried over into the second year of life by means of medical skill? But medicine cannot always surpass nature, and it

might indeed be possible that among cohorts with a low mortality during the first two years of life there will be an increase of death rate in the following three years of life.

Altogether, we may regard the weight of present evidence as altogether preponderant in favor of the view *that the death rate of the earliest period of life is selective—eliminating the weak and leaving the strong.* From our present point of view it adds another broad class of evidential material to the proof of the proposition that inheritance is one of the strongest elements, if not indeed the dominating factor, in determining the duration of life of human beings.

CHAPTER VII

EXPERIMENTAL STUDIES ON THE DURATION OF LIFE

INHERITANCE OF DURATION OF LIFE IN DROSOPHILA

In the last chapter there was presented indubitable proof that inheritance is a major factor in determining the duration of life in man. The evidence, while entirely convincing and indeed in the writer's opinion critically conclusive, must be, in the nature of the case, statistical in its nature. Experimental inquiries into the duration of human life are obviously impossible. It is always important, however, as a general principle, and particularly so in the present instance, to check one's statistical conclusions by independent experimental evidence. This can be successfully done, when one's problem is longevity, only by choosing an animal whose life-span relative to that of man is a short one, and in general the briefer it is, the better suited will the animal be for the purpose.

An organism which rather completely fulfils the requirements of the case, not only in respect of the shortness of the life span, but also in other ways, such as ease of handling, feeding, housing, etc., is the common "fruit" or "vinegar" fly, *Drosophila melanogaster*. This insect, which every one has seen hovering about bananas and other fruit in fruit shops, has lately attained great fame and respectability as a laboratory animal, as a result of the brilliant and extended investigations of Morgan and his students upon it, in an analysis of the mechanism of heredity. *Drosophila* is a small fly, per-

haps one fourth as large as the common house fly. It has striking red eyes, a brownish body, and wings of length and form varying in different strains. It lives normally on the surface of decaying fruit of all sorts, but because of a more or less well-marked preference for

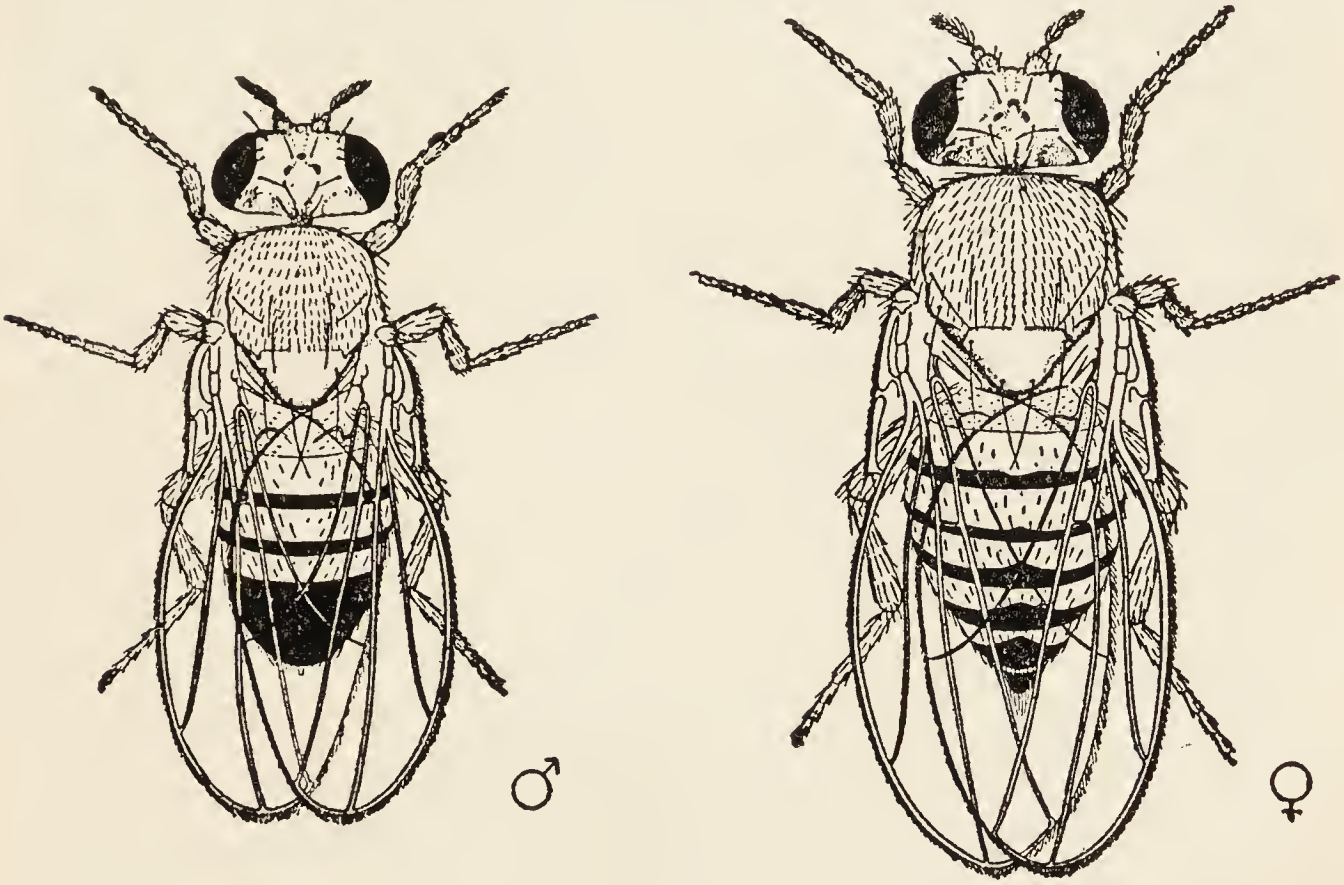


FIG. 46.—Male and female fruit fly. (*Drosophila melanogaster*). (From Morgan).

banana it is sometimes called the "banana" fly. While it lives on decaying fruit surfaces its food is mainly not the fruit itself, but the yeast which is always growing in such places.

The life cycle of the fly is as follows: The egg laid by the female on some fairly dry spot on the food develops in about 1 day into a larva. This larva or maggot crawls about and feeds in the rich medium in which it finds itself for about 3 to 4 days and then forms a pupa. From the pupa the winged imago or adult form emerges in about 4 or 5 days. The female generally begins to lay eggs within the first 24 hours after she is hatched. So

then we have about 8 to 10 days as the minimum time duration of a generation. The whole cycle from egg to egg, at ordinary room temperature, falls within this 10-day period with striking accuracy and precision.

The duration of life of the adult varies in an orderly manner from less than 1 day to over 90 days. The span

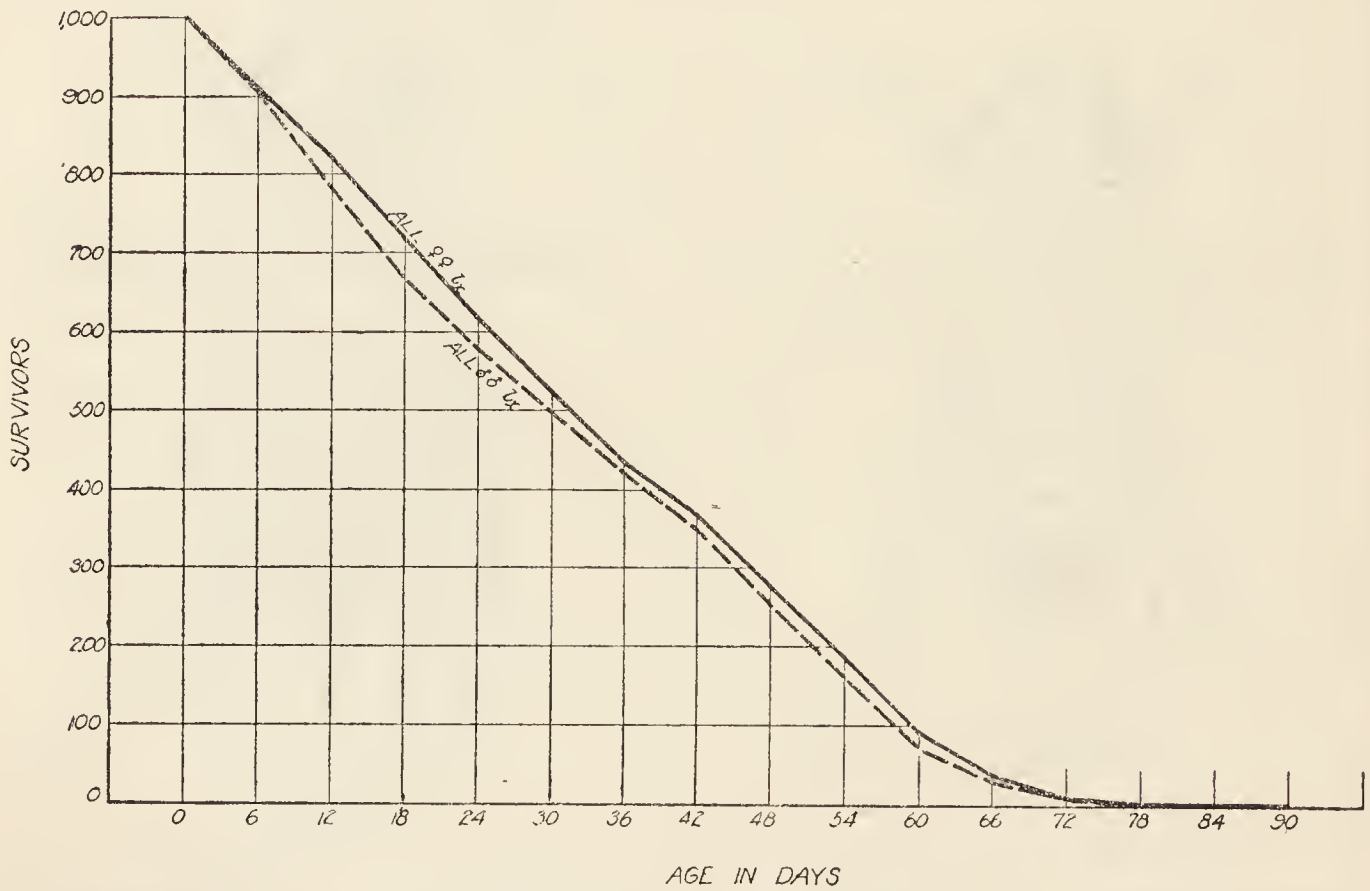


FIG. 47.—Life lines for *Drosophila melanogaster;* showing the survivors at different ages out of 1000 born at the same time.

of life of *Drosophila* quantitatively parallels in an extraordinary way that of man, with only the difference that life's duration is measured with different yardsticks in the two cases. Man's yardstick is one *year* long, while *Drosophila's* is one *day* long. A fly 90 days old is just as decrepit and senile, for a fly, as a man 90 years old is in human society.

This parallelism in the duration of life of *Drosophila* and man is well shown in Figure 47, which represents a life table for adult flies of both sexes. The survivorship, or l_x figures, are the ones plotted. The curves deal

only with flies in the adult or imago stage, after the completion of the larval and pupal periods. The curve is based upon 3,216 female and 2,620 male flies, large enough numbers to give reliable and smooth results. We note at once that in general the curve has the same form as the corresponding l_x curve from human mortality tables. The most striking difference is in the absence from the fly curves of the heavy infant mortality which characterizes the human curve. There is no specially sharp drop in the curve at the beginning of the life cycle, such as has been seen in the l_x curve for man in an earlier chapter in this book. This might at first be thought to be accounted for by the fact that the curve begins after the infantile life of the fly, but it must be remembered that the human l_x line begins at birth, and no account is taken of the mortality *in utero*. Really the larval and pupal stages of the fly correspond rather to the foetal life of a human being than to the infant life, so that one may perhaps fairly take the curves as covering comparable portions of the life span in the two cases and reach the conclusion that there is not in the fly an especially heavy incidence of mortality in the infant period of life, as there is in man. The explanation of this fact is, without doubt, that the fly when it emerges from the pupal stage is completely able to take care of itself. The baby is, on the contrary, in an almost totally helpless condition at the same relative age.

It is further evident that at practically all ages in *Drosophila* the number of survivors at any given age is higher among the female than among the males. This, it will be recalled, is exactly the state of the case in human mortality. The speed of the descent of the *Drosophila* curve slows off in old age, just as happens in the human life curve. The rate of descent of the curve in early middle life is somewhat more rapid with the flies than

in the case of human beings, but as will presently appear there are some strains of flies which give curves almost identical in this respect with the human mortality curves. In the life curves of Figure 47, all different degrees of inherited or constitutional variation in longevity are included together. More accurate pictures of the true state of affairs will appear when we come, as we presently shall, to deal with groups of individuals more homogeneous in respect of their hereditary constituents.

Having now demonstrated that the incidence of mortality is in general similar in the fly *Drosophila* to what it is in man, with a suitable change of unit of measure, we may proceed to examine some of the evidence regarding the inheritance of duration of life in this organism. The first step in such an examination is to determine what degree of natural variation of an hereditary sort exists in a general fly population in respect of this characteristic. In order to do this it is necessary to isolate individual pairs, male and female, breed them together and see whether, between the groups of offspring so obtained, there are genetic differences in respect of duration of life which persist through an indefinite number of generations. This approaches closely to the process called by geneticists the testing of pure lines. In such a process the purpose is to reduce to a minimum the *genetic* diversity which can possibly be exhibited in the material. In a case like the present, the whole amount of genetic variation in respect of duration of life which can appear in the offspring of a single pair of parents is only that which can arise by virtue of its prior existence in the parents themselves individually, and from the combination of the germinal variation existing in the two parents one with another. We may call the offspring, through successive generations, of a single pair of parents a line

of descent. If, when kept under identical environmental conditions, such lines exhibit widely different average durations of life, and if these differences reappear with constancy in successive generations, it may be justly concluded that the basis of these differences is hereditary in nature, since by hypothesis the environment of all the lines is kept the same. In consequence of the environmental equality, whatever differences do appear must be inherently genetic.

The manner in which these experiments are performed may be of interest. An experiment starts by placing two flies, brother and sister, selected from a stock bottle, together in a half-pint milk bottle. At the bottom of the bottle is a solidified, jelly-like mixture of agar-agar and boiled and pulped banana. On this is sown, as food, some dry yeast. A bit of folded filter paper in the bottle furnishes the larvae opportunity to pupate on a dry surface. About ten days after the pair of flies have been placed in this bottle, fully developed offspring in the imago stage begin to emerge. The day before these offspring flies are due to appear, the original parent pair of flies are removed to another bottle precisely like the first, and the female is allowed to lay another batch of eggs over a period of about nine days. In the original bottle there will be offspring flies emerging each day, having developed from the eggs laid by the mother on each of the successive days during which she was in the bottle. Each morning the offspring flies which have emerged during the preceding twenty-four hours are transferred to a small bottle. This has, just as the larger one, food material at the bottom and like the larger one is closed with a cotton stopper. All of the offspring flies in one of these small bottles are obviously of the same age, because they were born at the same time,

using this term "born" to denote emergence from the pupal stage as imagines. Each following day these small bottles are inspected. Whenever a dead fly is found, it is removed and a record made in proper form of the fact that its death occurred, and its age and sex are noted. Finally, when all the flies in a given small bottle have died, that bottle is discarded, as the record of the duration

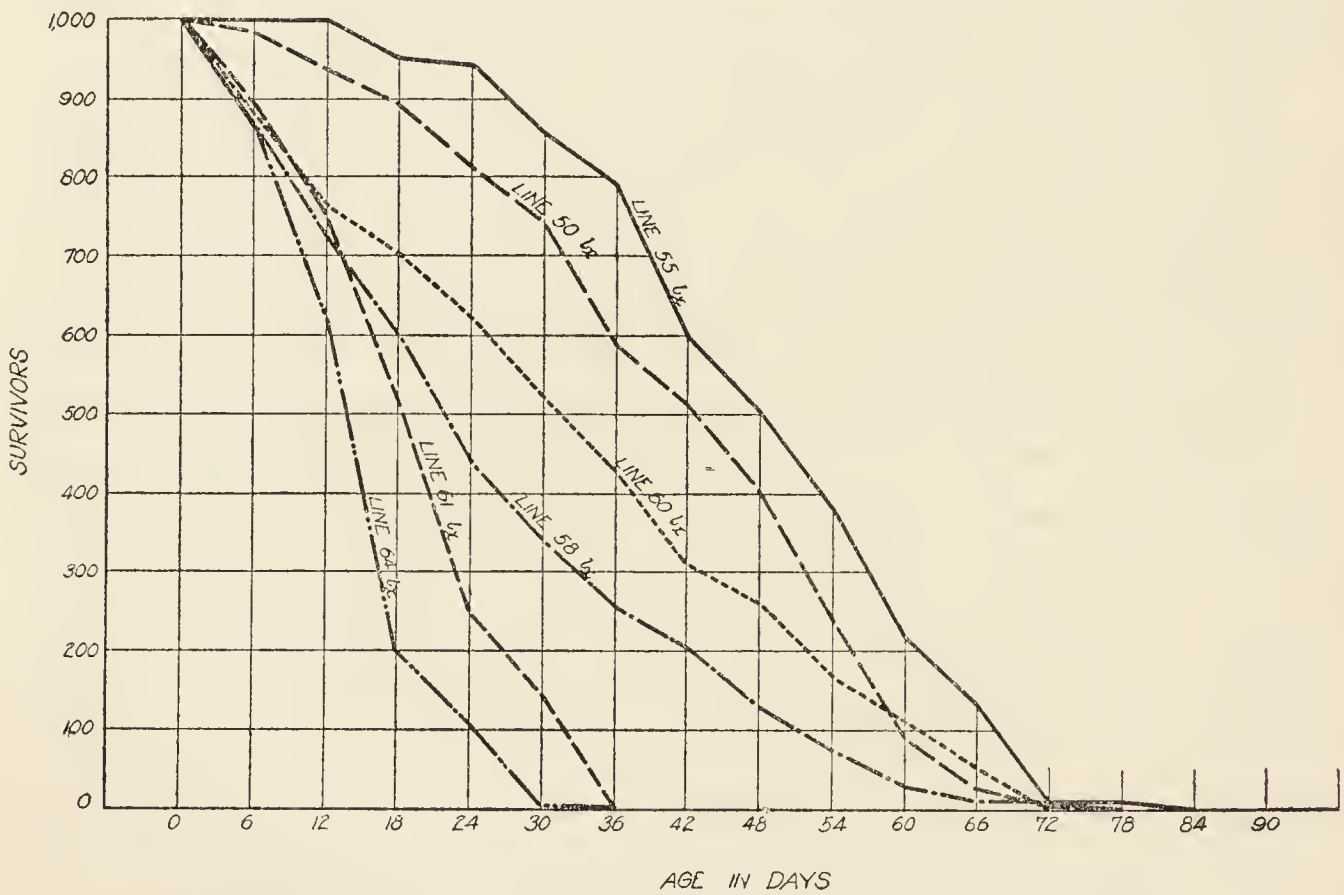


FIG. 48.—Life lines for different inbred lines of descent in *Drosophila*.

of life of each individual is then complete. All the bottles are kept in electric incubators at a constant temperature of 25° C., the small bottles being packed for convenience in wire baskets. All have the same food material, both in quality and quantity, so that the environmental conditions surrounding these flies during their life may be regarded as substantially constant and uniform for all.

Figure 48 shows the survival frequency, or l_x line of a life table, for six different lines of *Drosophila*, which have been bred in my laboratory. Each line represents

the survival distribution of the offspring of a single brother and sister pair mated together. In forming a line a brother and sister are taken as the initial start because by so doing the amount of genetic variation present in the line at the beginning is reduced to the lowest possible minimum. It should be said that in all of the curves in Figure 48, both male and female offspring are lumped together. This is justifiable for illustrative purposes because of the small difference in the expectation of life at any age between the sexes. The line of descent, No. 55, figured at the top of the diagram, gives an l_x line extraordinarily like that for man, with the exception of the omission of the sharp drop due to infantile mortality at the beginning of the curve. The extreme duration of life in this line was 81 days, reached by a female fly. The l_x line drops off very slowly until age 36 days. From that time on, the descent is more rapid until 72 days of age are reached when it slows up again. Lines 50, 60, and 58 show l_x curves all descending more rapidly in the early part of the life cycle than that for line 55, although the maximum degree of longevity attained is about the same in all of the four first curves. The general shape of the l_x curves changes however, as is clearly seen if we contrast line 55 with line 58. The former is concave to the base through nearly the whole of its course, whereas the l_x curve for line 58 is convex to the base practically throughout its course. While, as is clear from the diagram, the maximum longevity attained is about the same for all of these upper four lines, it is equally obvious that the mean duration of life exhibited by the lines falls off as we go down the diagram. The same process, which is in operation between lines 55 and 58, is continued in an even more marked degree in lines 61 and 64. Here not only is the descent more rapid in the early part of the

l_x curve, but the maximum degree of longevity attained is much smaller, amounting to about half of that attained in the other four lines. Both lines 61 and 64 tend to show in general a curve convex to the base, especially in the latter half of their course.

Since each of these lines of descent continues to show through successive generations, for an indefinite time, the same types of mortality curves and approximately the same average durations of life, it may safely be concluded that there are well marked hereditary differences in different strains of the same species of *Drosophila* in respect of duration of life. Passing from the top to the bottom of the diagram the average expectation of life is reduced by about two-thirds in these representative curves. For purposes of experimentation, each one of these lines of descent becomes comparable to a chemical reagent. They have standard durations of life, each peculiar to its own line and determined by the hereditary constitution of the individual in respect of this character. We may, with entire justification, speak of the flies of line 64 as hereditarily short-lived, and those of line 55 as hereditarily long-lived.

Having established so much, the next step in the analysis of the mode of inheritance of this character is obviously to perform a Mendelian experiment by crossing an hereditarily short-lived line with an hereditarily long-lived line, and follow through in the progeny of successive generations the duration of life. If the character follows the ordinary course of Mendelian inheritance, we should expect to get in the second offspring generation a segregation of different types of flies in respect of their duration of life.

Figure 49 shows the result of such Mendelian experi-

ment performed on a large scale. In the second line from the top of the diagram, labeled "Type I l_x," we see the mortality curve for an hereditarily long-lived pure strain of individuals. At the bottom of the diagram the "Type IV l_x" line gives the mortality curve for one of our hereditarily short-lived strains. Individuals of Type I and Type IV

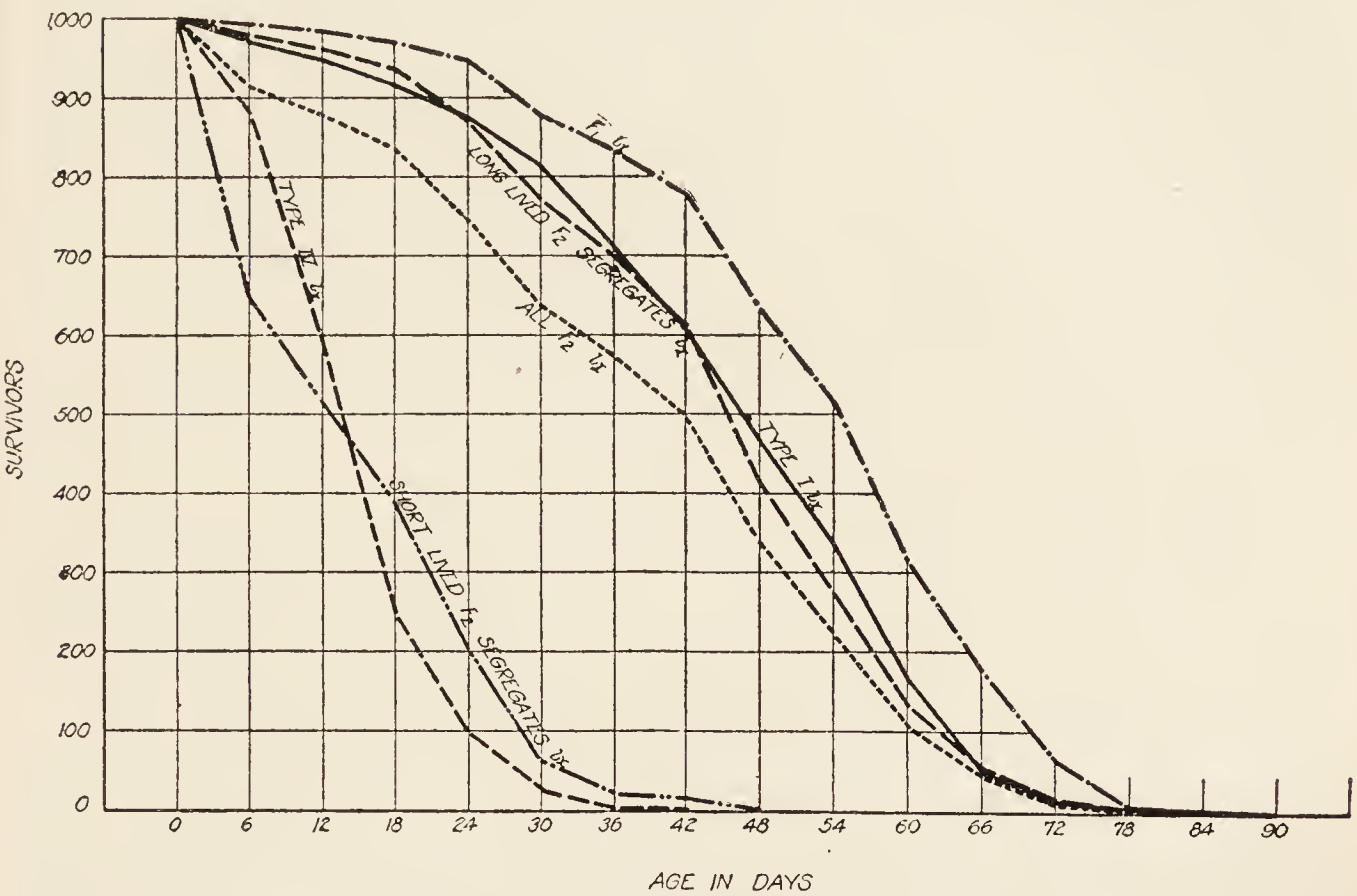


FIG. 49.—Life lines showing the result of Mendelian experiments on the duration of life in *Drosophila*. Explanation in text.

were mated together. The result in the first offspring hybrid generation is shown by the line at the top of diagram marked "F_1 l_x." The F_1 denotes that this is the mortality curve of the *first filial generation* from the cross. It is at once obvious that these first generation hybrids have a greater expectation of life at practically all ages than do either of the parent strains mated together to produce the hybrids. The result is exactly comparable to that which has for some time been known to occur in plants, from the researches particularly of East and others with maize. East and his students have worked

out very thoroughly the cause of this increased vigor of the first hybrid generation and show that it is directly due to the mingling of different germ plasms.

The average duration of life of the Type I original parent stock is 44.2 ± .4 days. The average duration of life of the short-lived Type IV flies is 14.1 ± .2 days, or only about one third as great as that of the other stock. The average duration of life of the first hybrid generation shown in the F_1 l_x line is 51.5 ± .5 days. So that there is an increase in average duration of life in the first hybrid generation, over that of the long-lived parent, of approximately 7 days. In estimating the significance of this, one should remember that a day in the life of a fly corresponds, as has already been pointed out, almost exactly to a year in the life of a man.

When individuals of the first hybrid generation are mated together to get the second, or F_2 hybrid generation we get a group of flies which, *if taken all together,* give the mortality curve shown in the line at about the middle of the diagram, labelled "All F_2 l_x." It, however, tells us little about the mode of inheritance of the character if we consider all the individuals of the second hybrid generation together, because really there are several kinds of flies present in this second hybrid generation. There are sharply separated groups of long-lived flies and of short-lived flies. These have been lumped together to give the "All F_2 l_x" line. If we consider separately the long-lived second generation group and the short-lived second generation group we get the results shown in the two lines labelled "Long-lived F_2 Segregates l_x," and "Short-lived F_2 Segregates l_x." It will be noted that the long-lived F_2 segregates have a mortality curve which almost exactly coincides with that of the original parent Type I stock. In other words, in the second generation after

the cross of the long-lived and short-lived types, a group of animals appears having almost identically the same form of mortality curve as that of one of the original parents in the cross. The mean duration of life of this long-lived second generation group is 43.3 ± .4 days, while that of the original long-lived stock was 44.2 ± .4 days. The short-lived F_2 segregates, shown at the bottom of the diagram, give a mortality curve essentially like that of the original short-lived parent strain. The two curves wind in and about each other, the F_2 flies showing a more rapid descent in the first half of the curve and a slower descent in the latter half. In general, however, the two are very clearly of the same form. The average duration of life of these short-lived second generation segregates is 14.6 ± .6 days. This, it will be recalled, is almost identically the same average duration of life as the original parent Type IV gave, which was 14.1 ± .2 days.

It may occur to one to wonder how it is possible to pick out the long-lived and short-lived segregates in the second generation. This is done by virtue of the correlation of the duration of life of these flies with certain external bodily characters, particularly the form of the wings, so that this arrangement of the material can be made with perfect ease and certainty.

These results show in a clear manner that duration of life, in *Drosophila* at least, is inherited essentially in accordance with Mendelian laws, thus fitting in with a wide range of other physical characters of the animal which have been thoroughly studied particularly by Morgan and his students. Such results as these just shown constitute the best kind of proof of the essential point which we are examining—namely, the fact that

duration of life is a normally inherited character. I do not wish at this time to go into any discussion of the details of the Mendelian mechanism for this character, in the first place, because it is too complicated and technical a matter for discussion here* and, in the second place, because the investigations are far from being completed yet. I wish here and now merely to present the demonstration of the broad general fact that duration of life is inherited in a normal Mendelian manner in these fly populations. The first evidence that this was the case came from some work of Dr. R. R. Hyde with *Drosophila* some years ago. The numbers involved in his experiment, however, were much smaller than those of the present experiments, and the preliminary demonstration of the existence of pure strains relative to duration of life in *Drosophila* was not undertaken by him. Hyde's results and those here presented are entirely in accord.

With the evidence which has now been presented regarding the inheritance of life in man and in *Drosophila* we may let that phase of the subject rest. The evidence is conclusive of the broad fact, beyond any question I think, coming as it does from such widely different types of life, and arrived at by such totally different methods as the statistical, on the one hand, and the experimental, on the other. We may safely conclude that the primary agent concerned in the winding up of the vital clock, and by the winding determining primarily and fundamentally how long it shall run, is heredity. The best insurance of longevity is beyond question a careful selection of one's parents and grandparents.

* Full technical details and all the numerical data regarding these and other *Drosophila* experiments referred to in this book will shortly be published elsewhere.

BACTERIA AND DURATION OF LIFE IN DROSOPHILA

But clocks may be stopped in other ways than by running down. It will be worth while to consider with some care a considerable mass of most interesting, and in some respects even startling, experimental data, regarding various ways in which longevity may be influenced by external agents. Since we have just been considering *Drosophila* it may be well to consider the experimental evidence regarding that form first. It is an obviously well-known fact that bacteria are responsible in all higher organisms for much organ breakdown and consequent death. An infection of some particular organ or organ system occurs, and the disturbance of the balance of the whole so brought about finally results in death. But is it not possible that we overrate the importance of bacterial invasion in determining, in general and in the broadest sense, the average duration of life? May it not be that when an organ system breaks down under stress of bacterial toxins, it is in part at least, perhaps primarily, because for internal organic reasons the resistance of that organ system to bacterial invasion has normally and naturally reached such a low point that its defenses are no longer adequate? All higher animals live constantly in an environment far from sterile. Our mouths and throats harbor pneumonia germs much of the time, but we do not all or always have pneumonia. Again it may fairly be estimated that of all persons who attain the age of 35, probably at least 95 per cent. have at some time or other been infected with the tubercle bacillus, yet fewer than one in ten break down with active tuberculosis.

What plainly is needed in order to arrive at a just estimate of the relative influence of bacteria and their

toxins in determining the average duration of life is an experimental inquiry into the effect of a bacteria-free, sterile mode of life. Metchnikoff has sturdily advocated the view that death in general is a result of bacterial intoxication. Now a bacteria-free existence is not possible for man. But it is possible for certain insects, as was first demonstrated by Bogdanow, and later confirmed by Delcourt and Guyenot. If one carefully washes either the egg or the pupa of *Drosophila* for 10 minutes in a strong antiseptic solution, say 85 per cent. alcohol, he will kill any germ which may be upon the surface. If the bacteria-free egg or pupa is then put into a sterile receptacle, containing only sterile food material and a pure culture of yeast, development will occur and presently an adult imago will emerge. Adult flies raised in this way are sterile. They have no bacteria inside or out. Normal healthy protoplasm is normally sterile, so what is inside the fly is bound to be sterile on that account, and by the use of the antiseptic solution what bacteria were on the outside have been killed.

The problem now is, how long on the average do such sterile specimens of *Drosophila* live in comparison with the ordinary fly, which is throughout its adult life as much beset by bacteria relatively as is man himself, it being premised that in both cases an abundance of proper food is furnished and that in general the environmental conditions, other than bacterial, are made the same for the two sets? Fortunately, there are some data to throw light upon this question from the experiments of Loeb and his associate Northrop on the duration of life in this form, taken in connection with experiments in the writer's laboratory.

Loeb and Northrop show that a sample of 70 flies, of the *Drosophila* with which they worked, which were

proved by the most careful and critical of tests to have remained entirely free of bacterial contamination throughout their lives, exhibited, when grown at a constant temperature of 25° C. *an average duration of life of* 28.5 *days.* In our experiments 2,620 male flies, of all strains of *Drosophila* in our cultures taken together, thus giving a fair random sample of genetically the whole *Drosophila* population, gave an average duration of life at the same constant temperature of 25° C. of 31.3 ±.3 days, and 3,216 females under the same temperature lived an average of 33.0 ± .2 days These were all non-sterile flies, subject to all the bacterial contamination incident to their normal laboratory environment, which we have seen to be a decaying germ-laden mass of banana pulp and agar. It is thought to be fairer to compare a sample of a general population with the Loeb and Northrop figures rather than a pure strain because probably their *Drosophila* material was far from homozygous in respect of the genes for duration of life.

The detailed comparisons are shown in Table 23.

TABLE 23

Average duration of life of Drosophila in the imago stage at 25° C.

Experimental group	Mean duration of life in days	Number of flies
Sterile (Loeb and Northrop)	28.5	70
Non-sterile, males, all genetic lines (Pearl)	31.3	2620
Non-sterile, females, all genetic lines (Pearl)	33.0	3216
Non-sterile, both sexes, all genetic lines (Pearl)	32.2	5836
Difference in favor of non-sterile	3.7	....
Probable error of difference about	± 1.0	....

We reach the conclusion that bacteria-free *Drosophila* live no longer on the average, and indeed perhaps even a little less long, under otherwise the same constant

environmental conditions, than do normal non-sterile—indeed germ-laden—flies. This result is of great interest and significance. It emphasizes in a direct experimental manner that in a *broad biological sense* bacteria play but an essentially accidental rôle in determining length of the span of life in comparison with the influence of heredity.

POVERTY AND DURATION OF LIFE

But we must take care lest we seem to convey the impression that no sort of environmental influence can affect the average duration of life. Such a conclusion would be manifestly absurd. Common sense tells us

FIG. 50.—Distribution of poverty in Paris (1911-13) as indicated by exemption from personal property tax. (After Hersch).

that environmental conditions in general can, and under some circumstances, do exert a marked influence upon expectation of life. A recent study of great interest and suggestiveness, if perhaps some lack of critical soundness, by the eminent Swiss statistician, Hersch, may be cited in this connection. Hersch became interested in the relation of poverty to mortality. He gathered

data from the 20 arrondissements of the city of Paris in respect of the following points, among others:

a. Percentage of families not paying a personal property tax.
b. Death rate per 1000 from all causes.
c. Stillbirths per 1000 living births.

Figure 50 shows in the black the percentage of families too poor to have any personal property tax assessed, first for each arrondissement separately, then at the

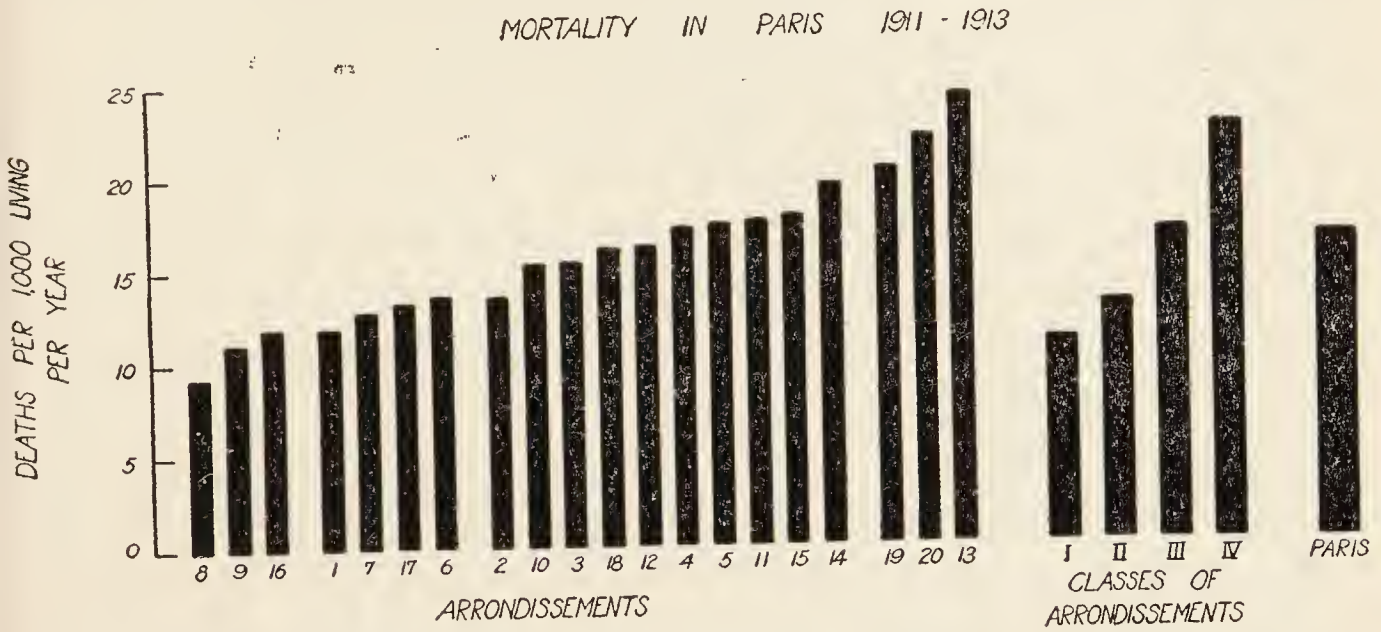


FIG. 51.—Death rates in Paris (1911-13) from all causes. (After Hersch).

right in broader bars for the four groups of arrondissements separated by wider spaces in the detailed diagram, and finally for Paris as a whole. It will be seen that the poverty of the population, measured by the personal property yardstick, is least at the left-hand end of the diagram, where the smallest percentages of families are exempted from the tax, and greatest at the right-hand end, where scarcely any of the population is well enough to do to pay this tax.

Figure 51 shows the death rates from all causes for the same arrondissements and the same groups. It is at once apparent that the black bars in this group run in a general manner parallel to the preceding one. The

poorest districts have the highest death rates, the richest districts the lowest death rates, and districts intermediate in respect of poverty are also intermediate in respect of mortality. On the face of the evidence there would seem to be here complete proof of the overwhelmingly important influence upon duration of life of degree of poverty, which is perhaps the most potent single environmental factor affecting civilized man to-day. But, alas, pitfalls proverbially lurk in statistics. Before we can accept this so alluring result and go along with our author to his final somewhat stupendous conclusion that if there were no poverty the death rate from certain important causes, as for example tuberculosis, would forthwith become *zero,* we must exercise a little inquisitive caution. What evidence is there that the inhabitants of the districts showing a high poverty rate are not *biologically* as well as economically differentiated from the inhabitants of districts with a low poverty rate? And again what is the evidence that it is not such biological differentiation rather than the economic which determines the death rate differences in the two cases? Unfortunately, our author gives us no whit of evidence on these obviously so important points. He merely assumes, because of the facts shown, that if some omnipotent spook were to transpose all the inhabitants of the Menilmontant arrondissement to the Elysee arrondissement, and *vice versa* for example, and were to permit each group to annex the worldly goods of the dispossessed group, then the death rates would be forthwith interchanged. There is no real evidence that any such result would follow at all. One cannot shake in the slightest degree from its solidly grounded foundation the critically determined fact of the paramount importance of the hereditary factor in determining rates of mortality, which have been summa-

rized in this and the preceding chapter by any such evidence as that of Hersch.

TABLE 24

Stillbirths in Paris (1911-13) by classes of arrondissements (Hersch)

Classes of Arrondissements	Absolute figures		Stillbirths per 100 living births
	Stillbirths	Living births	
I	1,004	12,313	8.2
II	1,390	19,998	7.0
III	7,279	82,821	8.8
IV	3,024	30,853	9.8
Paris	12,679	145,985	8.7

This, indeed, he himself finds to be the fact when he considers the extremely sensitive index of hereditary biological constitution furnished by the stillbirth rate. Table 24 gives the data. We see at once that there is no such striking increase in the fœtal mortality as we pass from the richest class of districts, as was shown in the death rate from all causes. Instead there is practically no change, certainly none of significance, as we pass from one class of districts to another. The rate is 8.2 per 100 living births in the richest class and 9.8 in the poorest.

Other definite evidence that such conclusion as those of Hersch cannot be accepted at anything like their face value is afforded by the work of Greenwood and Brown on the relation of poverty and the infant death rate. They find, giving subscripts the following meanings:

Subscript 1 = Birth rate
Subscript 2 = Artificial feeding rate
Subscript 3 = Poverty rate
Subscript 4 = Infant death rate

that

$$r_{34 \cdot 12} = .17 \pm .07$$

on the basis of the Bavarian data of Groth and Hahn.

Now this is a statistically insignificant net correlation, being less even than 3 times its probable error. It means that, when the birth rate and artificial feeding rate are held constant, differences in the infant death rate are not sufficiently influenced or determined by differences in the poverty rate to lead to a coefficient of correlation significantly different from zero, so far as Bavarian populations are indicative.

This result is further confirmed by an analysis which Greenwood and Brown made of Heron's London material, showing that in that case

$$r_{34.1} = .19 \pm .13$$

This coefficient means that the differences in infant mortality rate in the different districts of London, when the birth rate is made constant, are not associated with differences in poverty between the same districts to an extent sufficient to lead to a correlation coefficient sensibly different from zero.

Finally, Stevenson has, since the appearance of Hersch's paper, studied the same problems on the basis of the London data, for the sake of comparison with the results from Paris. He takes as the index of economic status the number of domestic servants (of both sexes) per 100 of population, and has examined the death rates from all causes, infant mortality, and tuberculosis for the identical years that Hersch used. The results are set forth in Table 24a.

Commenting on the facts regarding general mortality from all causes in London, Stevenson says:

"These bear an altogether different aspect from the Parisian figures. Whereas the latter increase so regularly with poverty that the highest rate for any district in one group never exceeds the lowest for any district in the next poorer group, in London the gradation, even for the groups themselves, is irregular, the lowest death-rate not being returned for the

TABLE 24a

Mortality of London boroughs grouped by wealth. (From Stevenson)

	Domestic servants (both sexes) per cent. of population (1911)	Death-rate from all causes, 1911-13		Infant mortality			Death-rate from tuberculosis, 1911-13	
				1918-19		1911-13		
		Crude	Standardized	Legitimate	Illegitimate	Total	Crude	Standardized
Kensington	16.67	13.7	13.6	83	221	112	1.32	1.32
Hampstead	16.40	10.4	11.0	64	236	72	0.81	0.80
Westminster	15.17	12.6	13.3	77	235	94	1.49	1.42
Chelsea	14.96	14.7	14.0	78	155	91	1.64	1.61
Marylebone	12.98	14.3	14.6	79	250	98	1.70	1.66
Paddington	10.42	13.3	13.2	88	237	109	1.33	1.31
Group I	14.38	13.2	13.4	80	228	100	1.39	1.36
City	6.46	14.0	14.6	122	278	97	1.95	1.84
Lewisham	5.71	11.3	11.1	51	294	84	1.09	1.01
Wandsworth	5.67	11.5	11.6	72	240	96	1.20	1.18
Stoke Newington	4.98	13.0	12.4	71	231	85	1.30	1.28
Holborn	4.38	15.1	15.2	99	267	102	2.30	2.17
Greenwich	4.10	13.9	13.7	93	349	102	1.60	1.59
Group II	5.34	12.2	12.1	73	272	94	1.32	1.30
Fulham	3.52	13.6	14.1	85	222	105	1.73	1.69
Hammersmith	3.30	14.5	14.3	91	207	114	1.62	1.58
Lambeth	3.18	14.3	14.0	82	217	105	1.71	1.68
St. Pancras	3.12	15.1	15.1	81	226	98	1.91	1.85
Hackney	2.95	13.5	13.6	83	355	100	1.68	1.67
Woolwich	2.81	12.6	12.9	88	220	84	1.67	1.65
Camberwell	2.68	13.8	13.6	83	268	99	1.61	1.60
Deptford	2.64	15.0	14.8	87	176	117	1.73	1.70
Battersea	2.62	13.6	13.7	74	276	107	1.56	1.53
Islington	2.48	14.9	14.5	88	258	107	1.69	1.66
Group III	2.90	14.1	14.0	84	243	103	1.70	1.67
Stepney	1.33	15.8	16.5	90	314	121	2.15	2.12
Finsbury	1.24	18.6	18.4	91	229	137	2.47	2.45
Southwark	1.23	17.5	17.6	101	225	122	2.23	2.17
Poplar	1.18	17.2	17.0	92	216	125	1.88	1.86
Bermondsey	0.97	17.8	17.8	105	360	133	2.35	2.31
Shoreditch	0.91	18.9	19.5	124	255	150	2.47	2.46
Bethnal Green	0.77	16.4	17.1	101	263	123	2.21	2.21
Group IV	1.13	17.1	17.4	99	260	128	2.21	2.18
County of London	4.74	14.4	14.4	86	247	109	1.71	1.68

richest group. Indeed, the difference between the first three London groups is slight, significant excess only being apparent for the poorest group. And whereas the excess of mortality of the poorest over the richest group in Paris is 104 per cent., in London it is only 30 per cent."

He then examines the question as to whether the discrepancies may be due to differences in the method of construction of the two sets of mortality figures and concludes:

"That the remarkable contrast in experience between the two cities cannot be explained, except possibly in a very minor degree, by any differences of method in compilation of the statistics compared."

Stevenson then goes on to the discussion of infant mortality and says:

"The conclusion just arrived at applies still more to infant than to total mortality, for, in its case, the contrast between rich and poor quarters of Paris assumes dimensions which, in the light of London experience, seem quite fantastic."

Regarding mortality from tuberculosis the London experience again fails to agree with the Paris experience, and Hersch's conclusions from the data of the latter city would be absurd if applied to the former.

EXPERIMENTS ON TEMPERATURE AND DURATION OF LIFE

Altogether it is plain that we need another kind of evidence than the simple unanalyzed parallelism which Hersch demonstrates between poverty and the general death rate if we are to get any deep understanding of the influence of environmental circumstances upon the duration of life or the general death rate. We shall do well to turn again to the experimental method. About a dozen years ago Loeb,

starting from the idea that chemical conditions in the organism are one of the main variables in this case, raised the question whether there was a definite coefficient for the duration of life and whether this temperature coefficient was of the order of magnitude of that of a chemical reaction. The first experiments were made on the unfertilized and fertilized eggs

of the sea urchin and could only be carried out at the upper temperature limits of the organism, since at ordinary temperatures this organism lives for years. In the upper temperature region the temperature coefficient for the duration of life was very high, probably on account of the fact that, at this upper zone of temperature, death is determined by a change of the nature of a coagulation or some other destructive process. Moore, at the suggestion of Loeb, investigated the temperature coefficient for the duration of life for the hydranth of a tubularian at the upper temperature limit and found that it was of the same order of magnitude as that previously found for the sea urchin egg. In order to prove that there is a temperature coefficient for the duration of life throughout the whole scale of temperatures at which an organism can live, experiments were required on a form whose duration of life was short enough to measure the duration of life even at the lowest temperature.

A suitable organism was found in *Drosophila*. This was grown under aseptic conditions, as already described. The general results are shown in Table 25.

TABLE 25

Effect of temperature on duration of life of Drosophila.
(After Loeb and Northrop)

Temperature	Duration (in days) of			
	Larval stage	Pupal stage	Life of imago	Total duration of life from egg to death
°C				
10	57	Pupæ die	120.5	$177.5 + x$
15	17.8	13.7	92.4	123.9
20	7.77	6.33	40.2	54.3
25	5.82	4.23	28.5	38.5
27.5	(4.15)	3.20	....	....
30	4.12	3.43	13.6	21.15

From this table it is seen that at the lowest temperature the duration of life is longest, and at the highest temperature shortest. Cold slows up the rate of living for the fly. Heat hastens it. One gathers, from the account which Loeb and Northrop give of the work, that at low temperature the flies are sluggish and inactive in all

three developmental stages and perhaps live a long time because they live slowly. At high temperatures, on the other hand, the fly is very active and lives its life through quickly at the pace that kills.'' These results are exactly comparable to the effect of a regular increase of temperature upon a chemical reaction. Indeed, Loeb and Northrop consider that their results prove that

> With a supply of proper and adequate food the duration of the larval stage is an unequivocal function of the temperature at which the larvæ are raised, and the temperature coefficient is of the order of magnitude of that of a chemical reaction, *i. e.*, about 2 or more for a difference of 10° C. It increases at the lower and is less at the higher temperatures. The duration of the pupal stage of the fly is also an unequivocal function of the temperature and the temperature coefficient is for each temperature practically identical with that for the larval stage. The duration of life of the imago is, with proper food, also an unequivocal function of the temperature and the temperature coefficient for the duration of life is, within the normal temperature limits, approximately identical with that for the duration of life of the larva and pupa.

How are these results to be reconciled with the previous finding that heredity is a primary factor in the determination of duration of life of *Drosophila?* We have here, on first impression at least, an excellent example of what one always encounters in critical genetic investigations: the complementary relations of heredity and environment. In our experiments a general mixed population of *Drosophila* kept under *constant environment* was shown to be separable by selection into a number of very diverse strains in respect of duration of life. In Loeb and Northrop's experiments, a general mixed population of *Drosophila,* but of presumably *constant genetic constitution,* at least approximately such, throughout the experiment, was shown to exhibit changes of duration of life with changing environments. It is the old familiar deadlock. Heredity constant plus changing

environment equals diversity. Environment constant plus varying hereditary constitution also equals diversity.

Can we penetrate no farther than this into the matter? I think in the present case we can. In Loeb and Northrop's experiments, temperature and duration of life were not the only two things that varied. The different temperature groups also differed from each other—*because* of the temperature differences, to be sure, but not less really—in respect of general metabolic *activity,* expressed in muscular movement and every other way. In the genetic experiments metabolic activity was substantially equal in all the hereditarily different lines. The idea suggests itself, both on *a priori* grounds and also upon the basis of certain experimental data presently to be in part reviewed, that possibly duration of life may be an implicit function of only the two variables

a. Genetic constitution
b. Rate of metabolic activity.

The functional relations of metabolic activity with temperature, food, light and other environmental factors are all well known. For present purposes we do not need to go into the question of their exact form. The essential point is that all these environmental factors stand in definite functional relations to rate of metabolic activity, and do not so stand in relation to genetic constitution. Genetic constitution is not a function of the environment, but is, for any individual, a constant, and only varies between individuals.

This may be thought merely to be an involved way of saying what one knows *a priori:* namely, that duration of life, in general and in particular, depends only upon heredity and environment. So in one sense it is. But the essential point I would make here is that the *manner*

in which the environmental forces (of sub-lethal intensity, of course) chiefly act in determining duration of life, appears to be by changing the rate of metabolism of the individual. Furthermore one would suggest, on this view, that what heredity does in relation to duration of life is chiefly *to determine, within fairly narrow limits, the total energy output which the individual can exhibit in its life time.* This limitation is directly brought about presumably through two general factors: *viz,* (a) the kind or quality of material of which this particular vital machine is built, and (b) the manner in which the parts are put together or assembled. Both of these factors are, of course, expressions of the extent and character of the processes of organic evolution which have given rise to this particular species about which we may be talking in a particular instance.

There is some direct experimental evidence, small in amount to be sure, but exact and pertinent, to the effect that the duration of life of an animal stands in inverse relation to the total amount of its metabolic activity, or put in other words, to the work, in the sense of theoretical mechanics, that it *as a machine* does during its life. Slonaker kept 4 albino rats in cages like the old fashioned revolving squirrel cages, with a properly calibrated odometer attached to the axle, so that the total amount of running which they did in their whole lives could be recorded. The results were those shown in Table 26.

It will be perceived that the amount of exercise taken by these rats was astonishingly large. For a rat to run 5,447 miles in the course of its life is indeed a remarkable performance. Now these 4 rats attained an average age at death of 29.5 months. But three control rats confined in stationary cages so that they could only

move about to a limited degree, but otherwise under conditions, including temperature, identical with those in the revolving cages, attained an average age at death of 40.3 months. All were stated to have died of "old

TABLE 26

Relation of longevity to muscular activity in rats (Slonaker)

TOTAL NUMBER OF MILES RUN DURING LIFE

Age in months at death	Rat No. 1 Miles	No. 4 Miles	No. 2 Miles	No. 3 Miles
25	1265			
26		1391		
32			2098	
34				5447

age." From this experiment it clearly appears that the greater the total work done, or total energy output, the shorter the duration of life, and *vice versa.* Or, put another way, if the total activity per unit of time is increased by some means other than increasing temperature, the same results appear as if the increased activity is caused by increased temperature. It appears, in short, to be activity *per se,* and not the temperature *per se* that is of real significance. There is other evidence, for which space lacks here, pointing in the same direction.

An entirely different, and extremely suggestive line of evidence in favor of the view here set forth, has been given by Professor Max Rubner, the distinguished German student of the energy relations of the living organism. Studying a considerable range of animals, he has found that all transform nearly the same total amount of energy, *per kilo of body weight,* in the whole period from their birth to their natural death. The mean value of the constant Rubner finds to be 191,600 calories, the values for different species ranging between 141,090 and

265,500 calories. Small animals, with an intensive metabolism live a relatively short time; large animals with more sluggish metabolism live a longer time. Rubner's view is that a definite sum of living action (energy transformation) determines the physiological end of life. This is precisely the view suggested here except that it is here postulated that the definite sum, for individual or species, is fundamentally determined by heredity, working through the structural make-up.

If we may be permitted to make a suggestion regarding the interpretation of Loeb and Northrop's results in conjunction with our own on *Drosophila,* it would be to this effect. Any given genetically pure strain of *Drosophila* is made up of individual machines, constructed to turn out, before breaking down, a definite limited amount of energy in the form of work, mechanical, chemical and other. This definitely limited total energy output is predetermined by the hereditary constitution of the individual which fixes the kind of physico-chemical machine that that individual is. But the *rate* per unit of time of the energy output may be influenced between wide limits by environmental circumstances in general and temperature in particular, since increased temperature increases rate of metabolic chemical changes in about the same ratio, as demonstrated by a wealth of work on temperature coefficients, as it increases other chemical changes. But if the rate of energy output per unit of time is changed, the total time taken for the total output of a predetermined amount of energy, as work, must change in inverse proportion to the change of rate. So we should expect just precisely the results on duration of life that Loeb and Northrop got, and so far from these results being in contradiction to ours upon heredity, they may be looked

upon as a necessary consequence of them. Loeb and Northrop's final conclusion is: "The observations on the temperature coefficient for the duration of life suggest that this duration is determined by the production of a substance leading to old age and natural death, or by the destruction of a substance or substances, which normally prevent old age and natural death." The view which I have here suggested, completely incorporates this view within itself, if we suppose that the total amount of hypothetical "substance or substances which normally prevent old age and natural death" was essentially determined by heredity.

This view I take to be in no way necessarily or fundamentally contradictory to that set forth in this work. Whatever the factor which determines specific longevity may be; whether a specific chemical substance, as Loeb and Northrop suggest, or more generally, as I have suggested, the kind of material, in the sense of its biological fitness, composing the multicellular body, and the nature of the organization (in detail) of that material to form the multicellular body; it seems to me that we have now a sufficient mass of critical evidence to say that it is proved that quantitatively the effective magnitude of this specific longevity factor in each particular case is *determined by heredity.* This I take to be of greater importance than the precise nature of the specific longevity factor itself, about which we are, admittedly, entirely ignorant. I can see nothing in the available evidence which definitely makes Loeb's suggestion inherently more probable than mine. It does, however, seem clear that, by definitely showing the significance of the heredity element in the problem, help has been rendered the progress of future research in the field.

It would seem, at first thought, that one should be able to test the theory here suggested, that rate of energy expenditure in the business of living is negatively correlated with the total duration of life, by an examination of the mortality rates for persons in different occupations as set forth, for example, in the well known paper of Bertillon. When one endeavors to make such a test, however, he is at once confronted with a series of difficulties which presently convince him that the project is virtually an impossible one, if he wishes critical results. In the first place, mean age at death will not do as a criterion, because of the great differences in the age distributions of those engaged in different occupations. This point has lately been thoroughly discussed by Collis and Greenwood, in their book "The Health of the Industrial Worker." Indeed, their whole treatment of the problem of occupational mortality is by far the most sound and critical which the present writer has yet seen. One must deal with age and sex specific death rates, or mortality indices based upon them.

In the second place, there are specific hazards, direct or indirect, in various occupations, quite apart from any question of energy expenditure involved in the case. These hazards will, obviously, tend to obscure any direct effects of the energy relations involved.

In the third place, we have only the merest suggestion of quantitatively accurate knowledge as to the average energy output involved in different trades and occupations.

On the last point, a beginning to collect information has been made by Waller and his co-workers. In a recent paper Waller and De Decker have given the mean calory output, per hour, per square meter of body surface for a small sample of workers in a few trades. But the re-

sults are far too meager, and, statistically, too unrepresentative to warrant any attempt at generalization from the present point of view.

As in so many other cases the experimental method is likely to shed far more critical light on this problem than is the purely statistical method dealing with human data. There are too many factors in the latter material that cannot be controlled.

GONADS AND DURATION OF LIFE

There is another and quite different line of experimental work on the duration of life which may be touched upon briefly. The daily press has lately had a great deal to say about rejuvenation, accomplished by means of various surgical procedures undertaken upon the primary sex organs, particularly in the male. This newspaper notoriety has especially centered about the work of Voronoff and Steinach. The only experiments which, at the present time, probably deserve serious consideration are those of Steinach. He has worked chiefly with white rats. His theory is that, by causing through appropriate operative procedure, an extensive regeneration, in a senile animal about to die, of certain glandular elements of the testis, senility and natural death will for a time be postponed because of the internal secretion poured into the blood by the regenerated "puberty glands" as he calls them. The operation which he finds to be most effective is to ligate firmly the efferent duct of the testis, through which the sperm normally pass, close up to the testis itself, and before the coiled portion of the duct is reached. The result of this, according to Steinach's account, is to bring about in highly senile animals a great enlargement of all the sex organs, a return of sexual activity, previously

lost through old age, and a general loss of senile bodily characteristics and a resumption of the conditions of full adult vigor in those respects, together with a considerable increase in the total duration of life.

Space is lacking to go into the many details of Steinach's work, much of which is indeed chiefly of interest only to the technical biologist, and from a wholly different standpoint than the present one. I should, however, like to present one example from his experiments. As control, a rat was taken, in the last degree senile. He was 26 months old when the experiment began. He was obviously emaciated, had lost much of his hair, particularly on the back and hind quarters. He was weak, inactive and drowsy, as indicated by the fact that his eyes were closed, and were, one infers from Steinach, kept so much of the time.

A litter brother of this animal had the efferent ducts of the testes ligated. This animal, we are told, was, at the time of the operation, in so much worse condition of senility than his brother, above described, that it was not thought worth while even to photograph him. His condition was considered hopeless. To the surprise of the operator, however, he came back, slowly but surely after the operation, and after three and a half months presented a perfect picture of lusty young rathood. He was in full vigor of every sort, including sexual. He outlived his brother by 8 months, and himself lived 10 months after the operation, at which time he was, according to Steinach, practically moribund. This represents a presumptive lengthening of his expected span of life by roughly a quarter to a third. *It is to be remembered, however, that Slonaker's rats to which nothing was done lived to an average age of 40 months.*

The presumption that Steinach's experiments have really brought about a statistically significant lengthening of life is large, and the basis of ascertained fact small. After a careful examination of Steinach's brilliant contribution, one is compelled to take the view that, however interesting the results may be from the standpoint of functional rejuvenation in the sexual sphere, the case is not proven that any really significant lengthening of the life span has occurred. In order to prove such a lengthening we must, first of all, have abundant and accurate quantitative data as to the normal variation of normal rats in respect of duration of life, and then show, having regard to the probable errors involved, that the mean duration of life after the operation has been significantly lengthened. This Steinach does not do. His paper is singularly bare of statistical data. We may well await adequate quantitative evidence before attempting any general interpretation of his results.

Indeed, one may note in passing that the case does not seem entirely clear in respect of Steinach's results in the purely sexual sphere. Thus Romeis has repeated the experiments, and finds, from comparative histological studies on the genital organs of rats, before and after Steinach's operation, that there is no evidence of any increase in Leydig's interstitial cells, and hence none of the so-called "interstitial or puberty gland." Romeis noted no increase in sexual desire among his rats after the operation. The hypertrophy of the seminal vesicles and prostate, described by Steinach following the operation, was also seen by Romeis, but found, by the latter, to be merely the result of the stasis of the secretions necessarily consequent upon the operation, and not a true functional hypertrophy at all.

THE PITUITARY GLAND AND DURATION OF LIFE

Robertson has been engaged for a number of years past on an extensive series of experiments regarding the effect of various agents upon the growth of white mice. The experiments have been conducted with great care and attention to the proper husbandry of the animals. In consequence, the results have a high degree of trustworthiness. In the course of these studies he found that the anterior lobe of the pituitary body, a small gland at the base of the brain, normally secretes into the blood-stream minute amounts of an active substance which has a marked effect upon the normal rate of growth. By chemical means, Robertson was able to extract this active substance from the gland in a fairly pure state, and gave to it the name *tethelin*. In later experiments, the effect of tethelin, given by the mouth with the food, was tried in a variety of ways.

In a recent paper, Robertson and Ray have studied the effect of this material upon the duration of life of the white mouse with the results shown in Table 27.

TABLE 27

Effect of tethelin on duration of life in days of white mice.

(*Robertson and Ray*)

	MALES				FEMALES				Both sexes together
Class of animals	Average duration of life	Dev. from normal	Dev. / P. E.	Chance dev. was accidental	Average duration of life	Dev. from normal	Dev. / P. E.	Chance dev. was accidental	Chance dev. was accidental
Normal	767	.....	.....	.....	719	.....	.....	.....	.....
Tethelin	866	+99	3.00	1:22.25	800	+81	2.25	1:6.75	1:150.2

From this table, it is apparent that the administration of tethelin with the food from birth to death prolonged

life to a degree which, in the case of the males, may be regarded as probably significant statistically. In the case of the females, where the ratio of the deviation to its probable error (Dev. / P. E.) falls to 2.25 the case is very doubtful. The procedure by which the chance of 1:150.2 that results in both sexes together were accidental, was obtained is of doubtful validity. Putting males and females together from the original table, I find the following results.

TABLE 28

Duration of life of white mice, both sexes taken together

(From data of Robertson and Ray)

Age Group	No. of deaths of normals (Both sexes)	No. of deaths of tethelin fed (Both sexes)	
200-299	3	..	Tethelin fed: Mean age at death =839±20
300-399	2	..	Normal fed: Mean age at death =743±17
400-499	2	1	Difference = 96±26
500-599	9	3	
600-699	7	9	$\frac{\text{Difference}}{\text{P. E. Diff.}} = 3.7$
700-799	15	..	
800-899	10	10	
900-999	10	6	
1000-1099	6	9	
1100-1199	..	1	
	64	39	

One concludes from these figures that tethelin can be regarded as having lengthened the span of life to a degree which is just significant statistically. One would expect, from the variation of random sampling alone, to get as divergent results as these about 1¼ times in every 100 trials with samples of 64 and 39, respectively.

In any event it is apparent that, making out the best case possible, the differences in average duration of life

produced by administration of tethelin are of a wholly different and smaller order than those which have been shown, in the earlier portion of this chapter, to exist between pure strains of *Drosophila* which are based upon hereditary differences.

Putting together all the results which have been reviewed in this and the preceding chapter, it appears to be clearly and firmly established that inheritance is the factor of prime importance in determining the normal, natural duration of life. In comparison with this factor, the influence of environmental forces (of sub-lethal immediate intensity of course) appears in general to be less marked.

CHAPTER VIII

NATURAL DEATH, PUBLIC HEALTH, AND THE POPULATION PROBLEM.

SUMMARY OF RESULTS

I have attempted to review some of the important biological and statistical contributions which have been made to the knowledge of natural death and the duration of life, and to synthesize these scattered results into a coherent unified whole. In the present chapter I shall endeavor to summarize, in the briefest way, the scattered facts which have been passed in review, and to follow a presentation of the general results to which they lead with some discussion of what we may reasonably regard the future as having in store for us, so far as may be judged from our present knowledge of the trend of events.

What are the general results of our review of the general biology of death? In the first place, one perceives that natural death is a relatively new thing, which appeared first in evolution when differentiation of cells for particular functions came into existence. Unicellular animals are, and always have been, immortal. The cells of higher organisms, set apart for reproduction in the course of differentiation during evolution, are immortal. The only requisite conditions to make their potential immortality actual are physico-chemical in nature and are now fairly well understood, particularly as a result of the investigations of Loeb upon artificial parthenogenesis and related phenomena. The essential and important

somatic cells of the body, however much differentiated, are also potentially immortal; but the conditions necessary for the actual realization of the potential immortality are, in the nature of the case, as has been shown by the brilliant researches of Leo Loeb, Harrison and Carrel on tissue culture, such as cannot be realized so long as these cells are actually in and a part of the higher metazoan body. The reason why this is so, and why in consequence death results in the metazoa, is that, in such organisms the specialization of structure and function necessarily makes the several parts of the body mutually dependent for their life upon each other. If one organ or group, for any accidental reason begins to function abnormally and finally breaks down, the balance of the whole is upset and death eventually follows. But the individual cells, themselves, could go on living indefinitely, if they were freed, as they are in cultures, of the necessity of depending upon the proper functioning of other cells for their food, oxygen, etc.

So then we see emerging, as our first general result, the fact that natural death is not a necessary or inevitable consequence of life. It is not an attribute of the cell. It is a by-product of progressive evolution—the price we pay for differentiation and specialization of structure and function.

This first result indicates logically, in any particular organism such as man, the great importance of a quantitative analysis of the manner in which different parts of the body break down and lead to death. Such an analysis, carefully worked through, demonstrates that this breaking down is not a haphazard process, but a highly orderly one resting upon a fundamental biological basis. The progress of the basic tissue elements

of the body along the evolutionary pathway appears to be an important factor in determining the time when the organ systems in which they are chiefly involved shall break down. Those organ systems that have evolved farthest away from original primitive conditions are the soundest and most resistant, and wear the longest under the strain of functioning. So then, the second large result is that it is the way potentially immortal cells are put together in mutually dependent organ systems that immediately determines the time relations of the life span.

But it was possible to penetrate more deeply into the problem than this by finding that the duration of life is an inherited character of an individual, passed on from parent to offspring, just as is eye color or hair color, and with a relatively high degree of precision. This has been proved in a variety of ways, first directly for man (Pearson) and for a lower animal, *Drosophila,* (Hyde, Pearl) by measuring the degree of hereditary transmission of duration of life, and indirectly by showing that the death rate was selective (Pearson, Snow, Bell, Ploetz) and had been, since nearly the beginning of recorded history, at least. It is heredity which determines the way the organism is put together—the organization of the parts. And it is when parts break down and the organization is upset that death comes. So the third large result is that heredity is the primary and fundamental determiner of the length of the span of life.

Finally, it is possible to say *probably,* though not as yet definitely because the necessary mass of experimental evidence is still lacking, but will, I believe, be shortly provided, that environmental circumstances play their

part in determining the duration of life largely, if not in principle entirely, by influencing the *rate* at which the vital patrimony is spent. If we live rapidly, like Loeb and Northrop's *Drosophila* at the high temperatures, our lives may be more interesting, but they will not be so long. The fact appears to be, though reservation of final judgment is necessary till more returns are in, that heredity determines the amount of capital placed in the vital bank upon which we draw to continue life, and which when all used up spells death; while environment, using the term in the broadest sense to include habits of life as well as physical surroundings, determines the rate at which drafts are presented and cashed. The case seems in principle like what obtains in respect of the duration of life of a man-constructed machine. It is self-evident that if, of two automobiles of the same make leaving the factory together new at the same time, one is run at the rate of 1,000 miles per year and the other at the rate of 10,000 miles per year, the useful life of the former is bound to be much longer in time that that of the latter, accidents being excluded in both cases. Again, a very high priced car, well-built of the finest material, may have a shorter duration of life than the poorest and cheapest machine, provided the annual mileage output of the former is many times that of the latter.

The first three of these conclusions seem to be firmly grounded. The last rests, at present, upon a less secure footing. Because it does, it offers an extremely promising field for both statistical and experimental research. We need a wide variety of investigations, like those of Loeb and Northrop, of Slonaker and of Rubner, on the experimental side. On the statistical side, well-conceived

and careful studies, by the most refined of modern methods, upon occupational mortality seem likely to yield large returns.

PUBLIC HEALTH ACTIVITIES

Fortunately, it is possible to get some light on the environmental side from existing statistical data by considering, in a broad general way, the results of public health activities. Any public health work, of course, deals, and can deal in the present state of public sentiment and enlightenment, only with environmental matters. Attempts at social control of the germ-plasm—the innate inherited constitutional make-up—of a people, by eugenic *legislation,* have not been conspicuously successful. And there is a good deal of doubt, having regard to all factors necessarily involved, whether they have always been even well-conceived. As an animal breeder of some years' experience, I have no doubt whatever that almost any breeder of average intelligence, if given omnipotent control over the activities of human beings, could, in a few generations, breed a race of men on the average considerably superior—*by our present standards*—to any race of men now existing in respect of many qualities or attributes. But, as a practical person, I am equally sure that nothing of the sort is going to be done by legislative action or any similar delegation of powers. Before any sensible person or society is going to entrust the control of its germ-plasm to politics or to science, there will be demanded that science know a great deal more than it now does about the vagaries of germ-plasms and how to control them. Another essential difficulty is one of standards. Suppose it to be granted that our knowledge of

genetics was sufficiently ample and profound to make it possible to make a racial germ-plasm exactly whatever one pleased; what individual or group of individuals could possibly be trusted to decide what it should be? Doubtless many persons of uplifting tendencies would promptly come forward prepared to undertake such a responsibility. But what of history? If it teaches us anything, it is that social, moral and political standards are not fixed and absolute, but vary, and vary radically in both space and time. And further, history teaches that a great many of the most valuable people, in the highest and best sense, whom the world has ever known, were so constituted physically, morally, or otherwise, as to make it certain that under a strict eugenic regime they never would have existed at all. One cannot but feel that man's instinctive wariness about experimental interferences with his germ-plasm is in considerable degree, well-founded.

But because of the altogether more impersonal nature of the case, most men individually and society in general are perfectly willing to let anybody do anything they like in the direction of modifying the environment in what is believed, or hoped to be, the direction of improvement, or trying to, quite regardless of whether science is able to give any slightest inkling on the basis of ascertained facts as to whether the outcome will be good, bad or indifferent. Hence many kinds of weird activities and propaganda flourish like the proverbial bay tree.

Of all organized activities looking towards the direct modification of the environment to the benefit of mankind, that group comprised under the terms sanitation, hygiene

and public health have, by all odds, the best case when measured in terms of accomplishment. Man's expectation of life has increased as he has come down through the centuries (*cf.* Pearson and Macdonell.) A large part of this improvement must surely be credited to his improved understanding of how to cope with an always more or less inimical environment and assuage its asperities to his greater comfort and well-being. To fail to give this credit would be manifestly absurd.

But it would be equally absurd to attempt to maintain that all decline in the death-rate which has occurred has been due to the efforts of health officials, whether conscious or unconscious, as is often asserted and still more often implied in the impassioned outpourings of zealous propagandists. The open-minded student of the natural history of disease knows perfectly well that a large part of the improvement in the rate of mortality cannot possibly have been due to any such efforts. To illustrate the point, I have prepared a series of illustrations dealing with conditions in the Registration Area of the United States in the immediate past. All these diagrams (Figures 52, 53, and 54) give death-rates per 100,000 from various causes of death in the period of 1900-1918, inclusive, both sexes for simplicity being taken together. The lines are all plotted on a logarithmic scale. The result of this method of plotting is that the slope trend of each line is directly comparable with that of any other, no matter what the absolute magnitude of the rates concerned. It is these slopes, measuring improvement in mortality, to which I would especially direct attention.

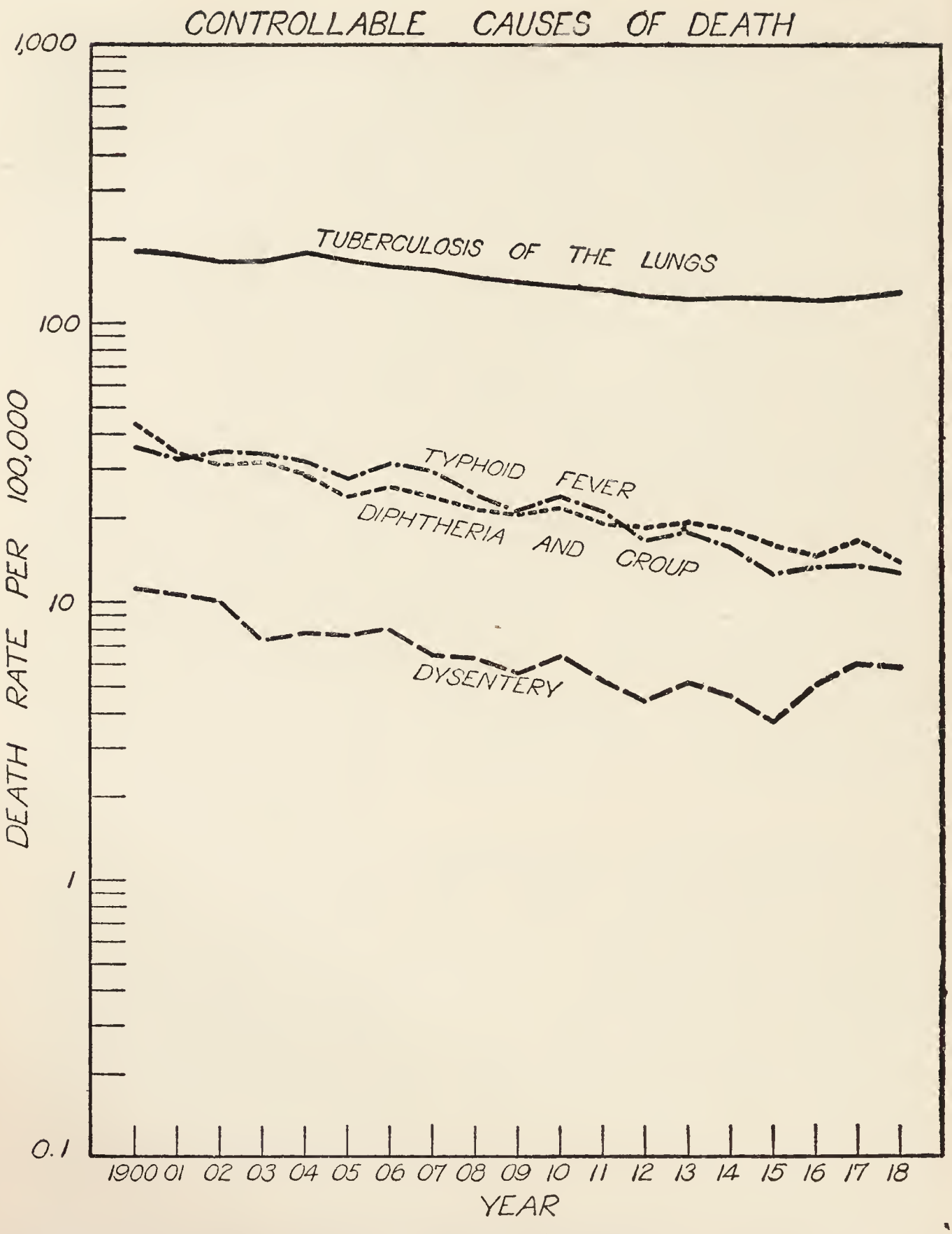


FIG. 52.—Trend of death rates for four causes of death against which public health activities have been particularly directed.

In figure 52 are given the trends of the death-rates for four diseases against which public health and sanitary activities have been particularly and vigorously

directed, with, as we are accustomed to say, most gratifying results. The diseases are:

1. Tuberculosis of the lungs.
2. Typhoid fever.
3. Diphtheria and croup.
4. Dysentery.

We note at once that the death-rates from these diseases have all steadily declined in the 19 years under review. But the rate of drop has been slightly unequal. Remembering that the slopes are comparable, wherever the lines may lie, and that an equal slope means a *relatively* equally effective diminution of the mortality of the disease, we note that the death-rate from tuberculosis of the lungs has decreased slightly less than any of the other three. Yet it may fairly be said that so strenuous a warfare, or one engaging in its ranks so many earnest and active workers, has probably never in the history of the world been waged against any disease as that which has been fought in the United States against tuberculosis in the period covered. The rates of decline of the other three diseases are all practically identical.

Figure 53 shows entirely similar trends for four other causes of death—namely:

1. Bronchitis (acute and chronic).
2. Paralysis without specified cause.
3. Purulent infection and septicæmia.
4. Softening of the brain.

Now it will be granted at once, I think, that public health and sanitation can have had, at the utmost, extremely little, if anything, to do with the trend of mortality from these four causes of death. For the most part they certainly represent pathological entities far beyond the present reach of the health officer. Yet the

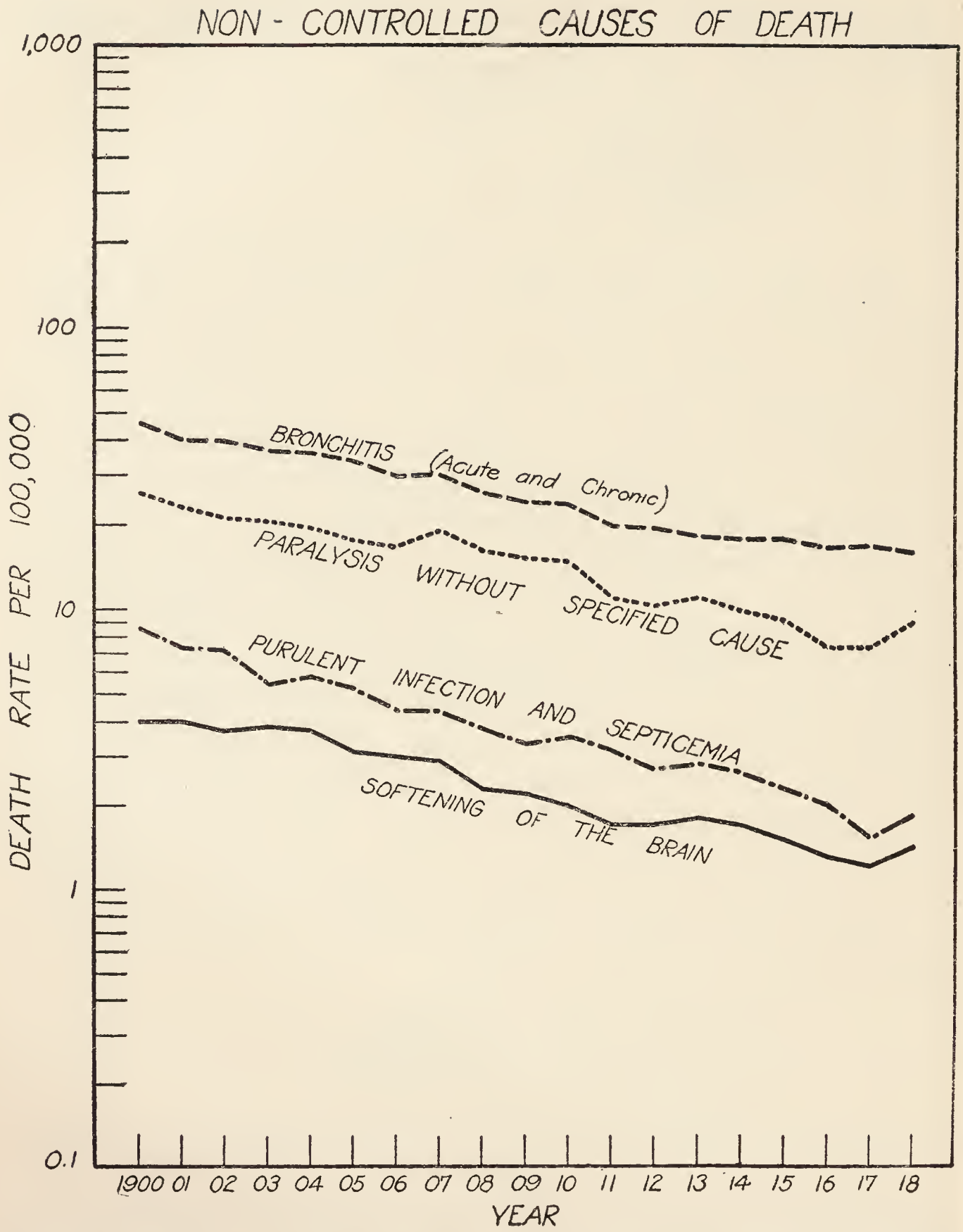


Fig. 53.—Trend of death rates from four causes of death upon which no direct attempt at control has been made.

outstanding fact is that their rates of mortality have declined and are declining just as did those in the controllable group shown in Figure 52. It is of no moment

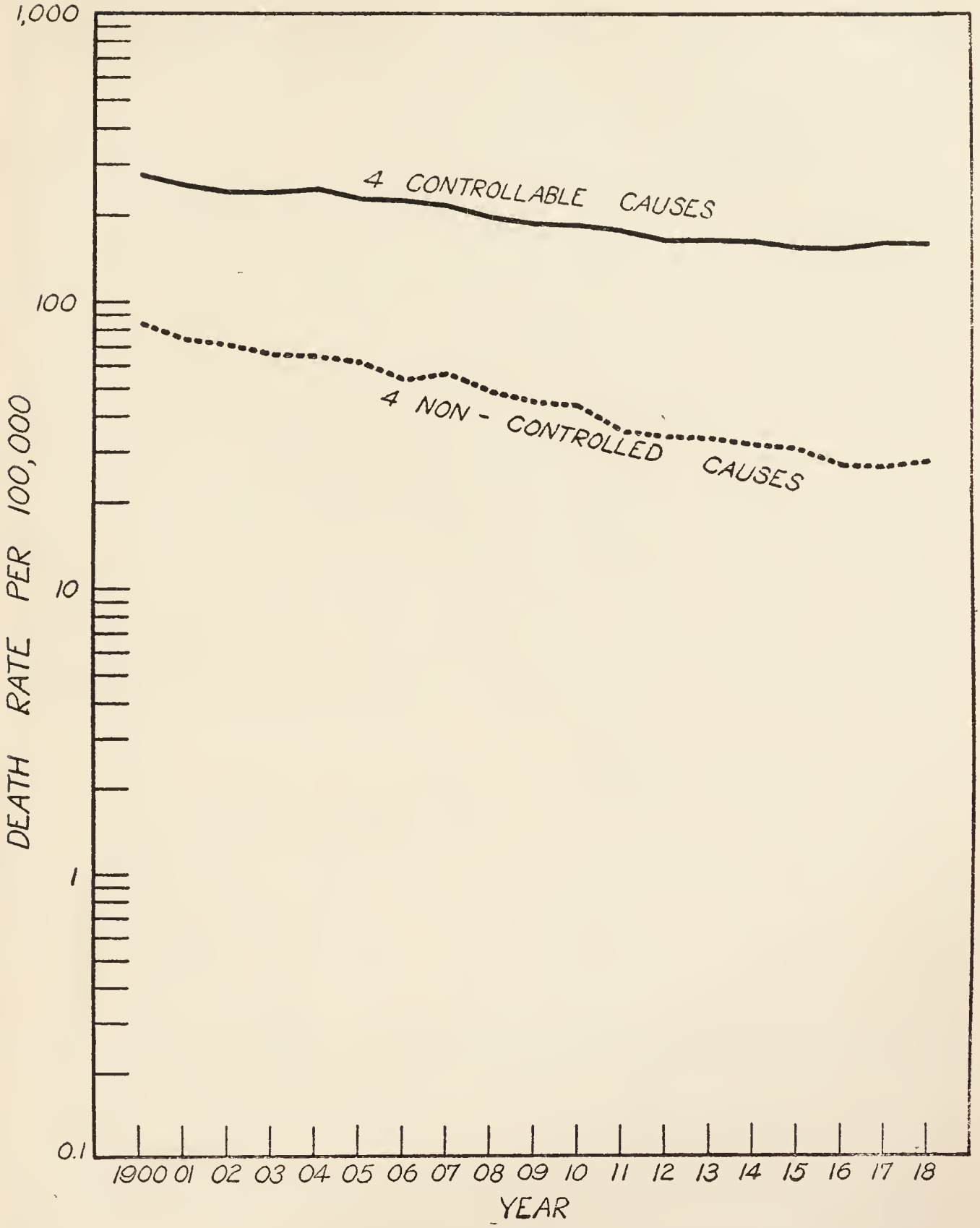


FIG. 54.—Trend of combined death rate from the four causes shown in Figure 52 as compared with the four causes shown in Figure 53.

to say that the four causes of death in the second group are *absolutely* of less importance than some of those in the first group, because what we are here discussing is not relative force of mortality from different causes,

but rather the *trend* of mortality from particular causes. The *rate* of decline is just as significant, whatever the absolute point from which the curve starts.

It is difficult to carry in the mind an exact impression of the slope of a line, so, in order that a comparison may be made, I have plotted in Figure 54, first, the total rate of mortality from the four controllable causes of death taken together and, second, the total rate of mortality from the four uncontrolled causes taken together. The result is interesting. The two lines were actually nearer together in 1900 than they were in 1918. They have diverged because the recorded mortality from the uncontrolled four has actually decreased faster in the 19 years than has that from the four against which we have been actively fighting. The divergence is not great, however. Perhaps we are only justified in saying that the mortality in each of the two groups has notably declined, and at not far from identical rates.

Now the four diseases in this group, I chose quite at random from among the causes of death whose rates I knew to be declining, to use as an illustration solely. I could easily pick out eight other causes of death which would illustrate the same point. I do not wish too much stress to be laid upon these examples. If they may serve merely to drive sharply home into the mind that it is only the tyro or the reckless propagandist, long ago a stranger to truth, who will venture to assert that a declining death-rate *in and of itself* marks the successful result of human effort, I shall be abundantly satisfied.

It has been objected that the decline shown by the four "non-controlled" causes in the example just dealt with is due wholly, or nearly so, to changes in the practice of physicians relative to the reporting of the cause of

death, and that, therefore, the decline is spurious. I have not been able to find that there is any good evidence that this is the fact; that, in short, changes in reporting practice have affected the "non-controlled" group more than the "controllable" group. But another kind of example may be cited to illustrate the same general point. Suppose we compare the course of mortality from certain well-defined causes, about the reporting of which there can be no controversy, in (a) a group of countries standing in an advanced position in matters of public health, sanitation, etc., and (b) a group of countries relatively backward and undeveloped in these respects. Such a comparison is impossible to make over any long period of time because of lack of comparable data. I have succeeded in getting comparable statistics on two diseases, namely typhoid fever and diphtheria, for the period 1898 to 1912 inclusive, for the following countries:

A. Countries having (in period covered) highly developed public health and sanitation.	B. Countries having (in period covered) less highly developed public health and sanitation than those in group A.
Australia	Italy
Austria	Jamaica
England and Wales	Roumania
Germany	

Without going into detailed comparisons, which might be thought invidious, it is evident on the face of the case, I think, that the countries in the A group were, on the average during the period covered, much more advanced in all practical public health matters than were the countries in group B.

In Figures 55 and 56 are shown the trends of the weighted average death rates from typhoid fever and diphtheria respectively in the two groups of countries.

It is evident from these diagrams that the death rates

from these two causes declined, during the period covered, in both the A and the B groups of countries and at not far from the same rate. There is no such large difference as would be expected if organized human interference with the natural history of disease always played

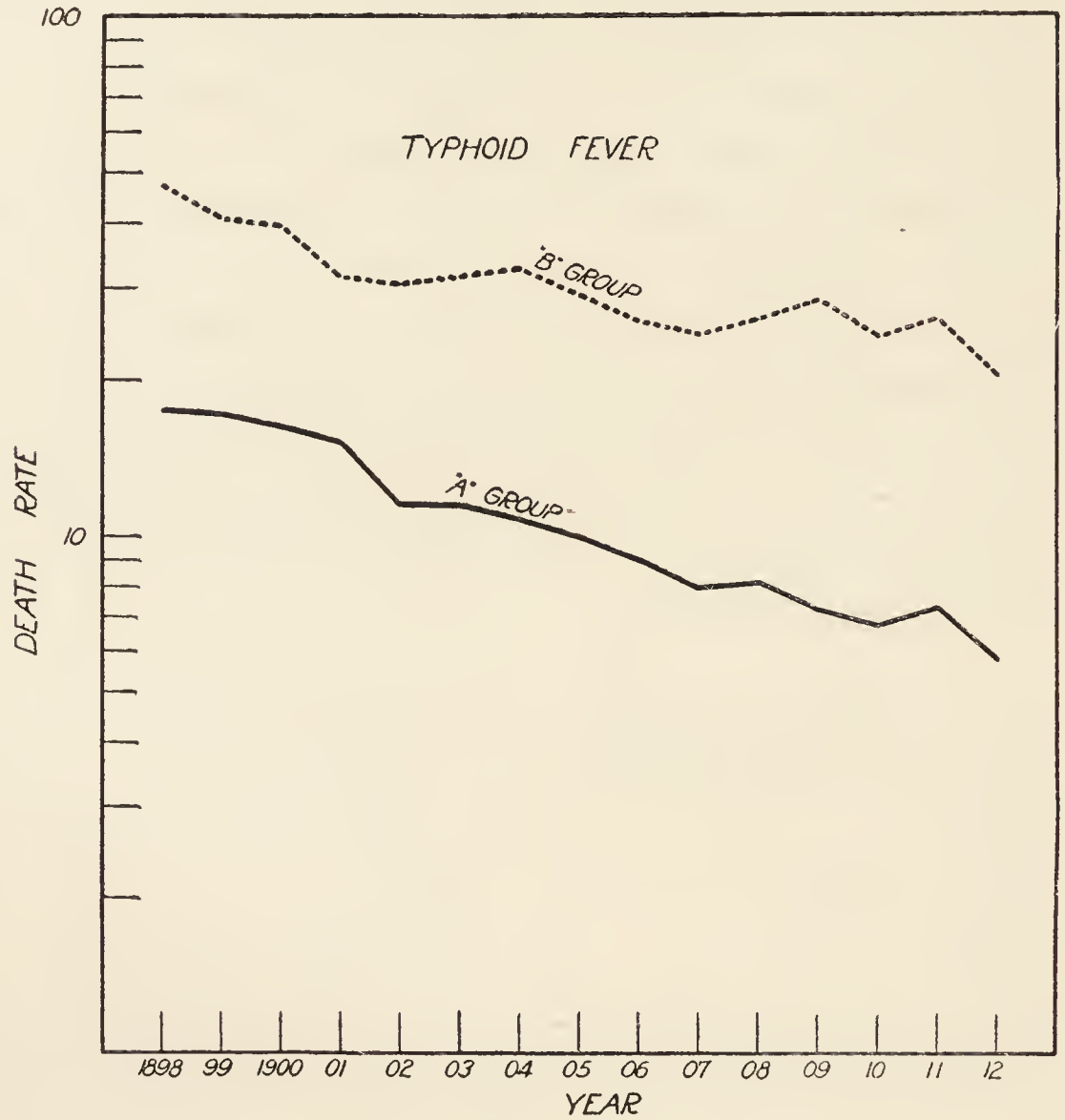


Fig. 55.—Course of the weighted average death rate, for the countries in the A (solid line) and B (broken line) groups, from typhoid fever.

the rôle of immediate and large importance which the propagandist asserts that it does.

To guard against the possibility of any misunderstanding, let me say quite specifically and categorically, that the above is not intended in any way to convey the idea that public health work is not desirable, or that a

laissez-faire policy would be better, or that public health efforts have not been enormously valuable in connection with typhoid fever and diphtheria. My purpose is quite other, being solely a desire to emphasize two things, *viz:*

1. That the trend of human mortality in time is an

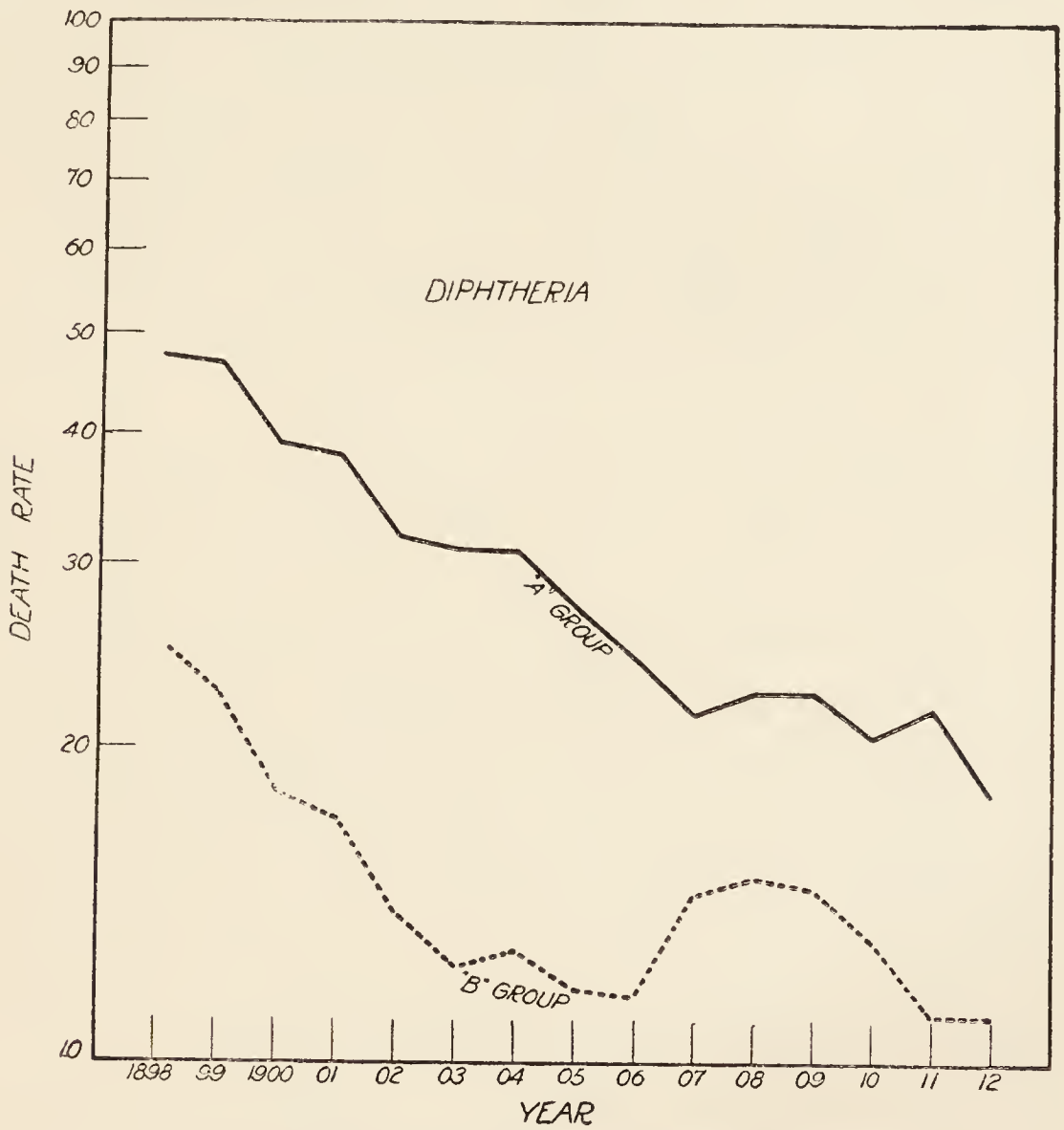


Fig. 56.—Like figure 55, but for diphtheria and croup.

extraordinarily complex biological phenomenon, in which many factors besides the best efforts of health officials are involved.

2. That for many causes of death a vast lot needs to be added to our knowledge of etiology, in the broadest sense, before really efficient control can be hoped for. This knowledge can come only through scientific investi-

gation, and not through the complacent acceptance of the propagandist's assurance that "if what knowledge we now have is applied, all will be well."*

Many others have, of course, perceived that, in the natural history of disease, mortality from particular causes may decline over long periods of time without any relation to what health departments have done, or tried to do about it. For example, Given has recently pointed out that there is no evidence that anything that man has done has affected, in either one way or the other, the decline in the mortality of tuberculosis, which has been continuous for nearly three-quarters of a century. Pearson has discussed the same point.

There is much in our public health work that is worthy of the highest praise. When based upon a sound foundation of ascertained fact it may, and does, proceed with a step as firm and inexorable as that of Fate itself, to the wiping out of preventable mortality. Two recent examples may be cited here, by way of specific illustration of what real and reasonably complete scientific knowledge can accomplish in public health work. Both examples are taken from the work of the International Health Board of the Rockefeller Foundation, with the permission of its director, Mr. Wickliffe Rose.

The first concerns malaria. The life cycle of the malaria parasite is definitely known, and furnished a

---

* One can but wonder if the many scientific men, who permit, and to some extent approve, such assertions, have ever thought of the menace to the continued support of research in science in general which inheres in this attitude of mind. The support of research comes finally back always to society in general—to the "average citizen" in short. Is it the part of wisdom to leave his education as to the meaning and significance of science for his happiness and well-being, so entirely in the hands of the propagandist as we now do? Has anti-vivisection taught no lesson?

definite scientific basis for control procedure. "It is well understood, not only by scientists, but also by intelligent laymen, that the spread of the infection may be prevented by mosquito control, by protecting people from being bitten by mosquitoes, or by destroying the parasite in the blood of the human carrier. It has been shown, moreover, by repeated demonstrations, that by application of any one of these measures, or of any combination of them, the amount of malaria in a community may be reduced indefinitely. There are few diseases that present so many vulnerable points of attack and none perhaps the control of which may be made more definite or certain." (Rose).

In 1916 the International Health Board undertook some experiments in control at Crossett, Ark. In describing the work Rose says:

"Effort has been made to test the feasibility of malaria control in small communities by resort to such simple anti-mosquito measures as would fall within the limits of expenditure that such communities might well afford. The habits of the three mosquitoes—*A. quadrimaculatus* Say, *A. punctipennis* Say, and *A. cruzians* Wiedermann—which are responsible for the infection in these communities have been made the subject of constant study with a view to eliminating all unnecessary effort, and thereby reducing cost.

"Experiment at Crossett, 1916—The first of these tests was undertaken at Crossett, a lumber town of 2,129 inhabitants, situated in Ashley County in south-eastern Arkansas, about 12 miles north of the Louisiana line. Crossett lies at the edge of the so-called "uplands," in a level, low-lying region (elevation 165 feet), with sufficient undulation to provide reasonably good natural drainage. Climatic conditions and abundant breeding places favor the propagation of *anopheles*. Malaria, in its severe form, is widely prevalent as an endemic infection, and according to the estimate of local physicians, is the cause of about 60 per cent. of all illness throughout the region. Within the town itself the malaria rate was high, and was recognized by the lumber corporation and the people as a serious menace to health and working efficiency.

"The initial step in the experiment was a survey of the community to determine the malaria incidence, to ascertain in the species of mosquitoes

responsible for the spread of the infection, and to locate the breeding places of these mosquitoes. Breeding places were exhibited on a community map, and organized effort was centered on their destruction or control. The program of simple measures excluded all major drainage. Barrow pits and shallow ponds were filled or drained; streams were cleared of undergrowth when necessary to let the sunlight in; their margins and beds were cleared of vegetation and obstruction; and they were trained to a narrow channel, thus providing an unobstructed off-flow. Artificial containers were removed from premises; water barrels on bridges were treated with nitre cake. All remaining breeding places were regularly treated by removing vegetation, opening up shallow margins to give free access to small fish, and spraying once a week with road oil by means of automatic drips or a knapsack sprayer. All operations were under the supervision of a trained lay inspector. Care was exercised to eliminate all unnecessary effort and to secure, not the elimination of the last mosquito, but a reasonably high degree of control at a minimum cost."

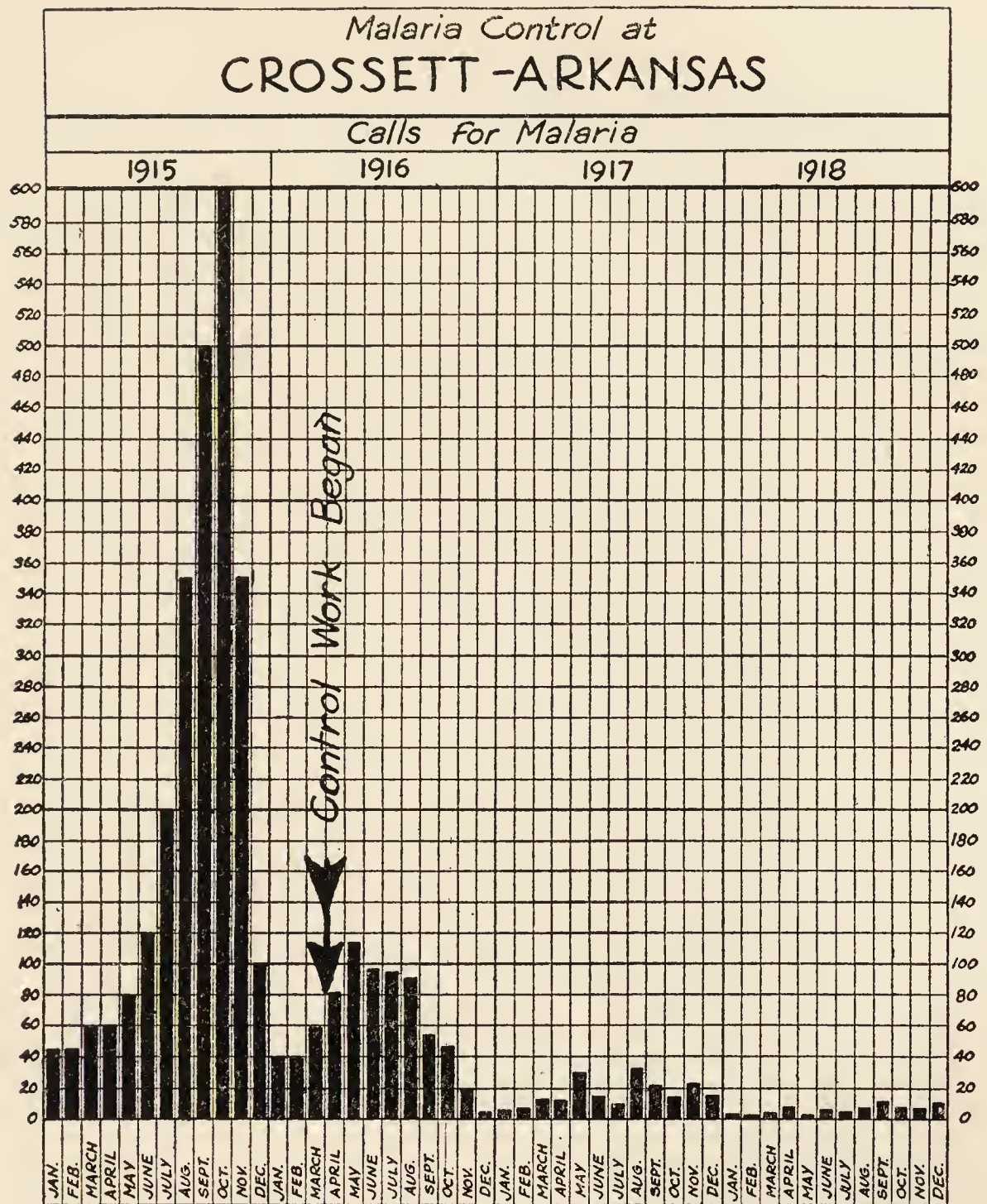
The results are shown in Figure 57, as measured by a number of physicians' calls for the treatment of malaria in the community.

The second example shows the effectiveness of control of yellow fever, another disease for which definite scientific knowledge exists as to etiology and mode of transmission.

Nothing could more convincingly demonstrate than does Figure 58 the effectiveness with which this disease can be controlled. The diagram shows the results of the International Health Board's yellow fever work in Guayaquil in 1918-1920.

THE POPULATION PROBLEM

Turning to another phase of the problem, it is apparent that if, as a result of sanitary and hygienic activities and natural evolution, the average duration of human life is greater now than it used to be and is getting greater all the time, then clearly there must be more people on the earth at any time, out of a given number



Monthly Distribution of Calls

	1915	1916	1917	1918
JAN.	45	40	6	3
FEB.	45	39	7	2
MARCH	58	59	13	4
APRIL	60	81	12	8
MAY	80	114	31	2
JUNE	120	98	15	6
JULY	200	95	9	5
AUG.	350	91	33	7
SEPT.	500	54	22	11
OCT.	600	46	14	8
NOV.	350	20	23	7
DEC.	100	4	15	10

Population, 2029

Total Calls ·	1915 -	2500
	1916 -	741
	1917 -	200
	1918 -	73
Percentage of Reduction, 1915-1918		97.1
Per Capita Cost:		
	1916 -	1.24
	1917 -	.63
	1918 -	.53

FIG. 57.—Record of malaria control by anti-mosquito measures, Crossett, Ark. 1916-1918. (From Rose).

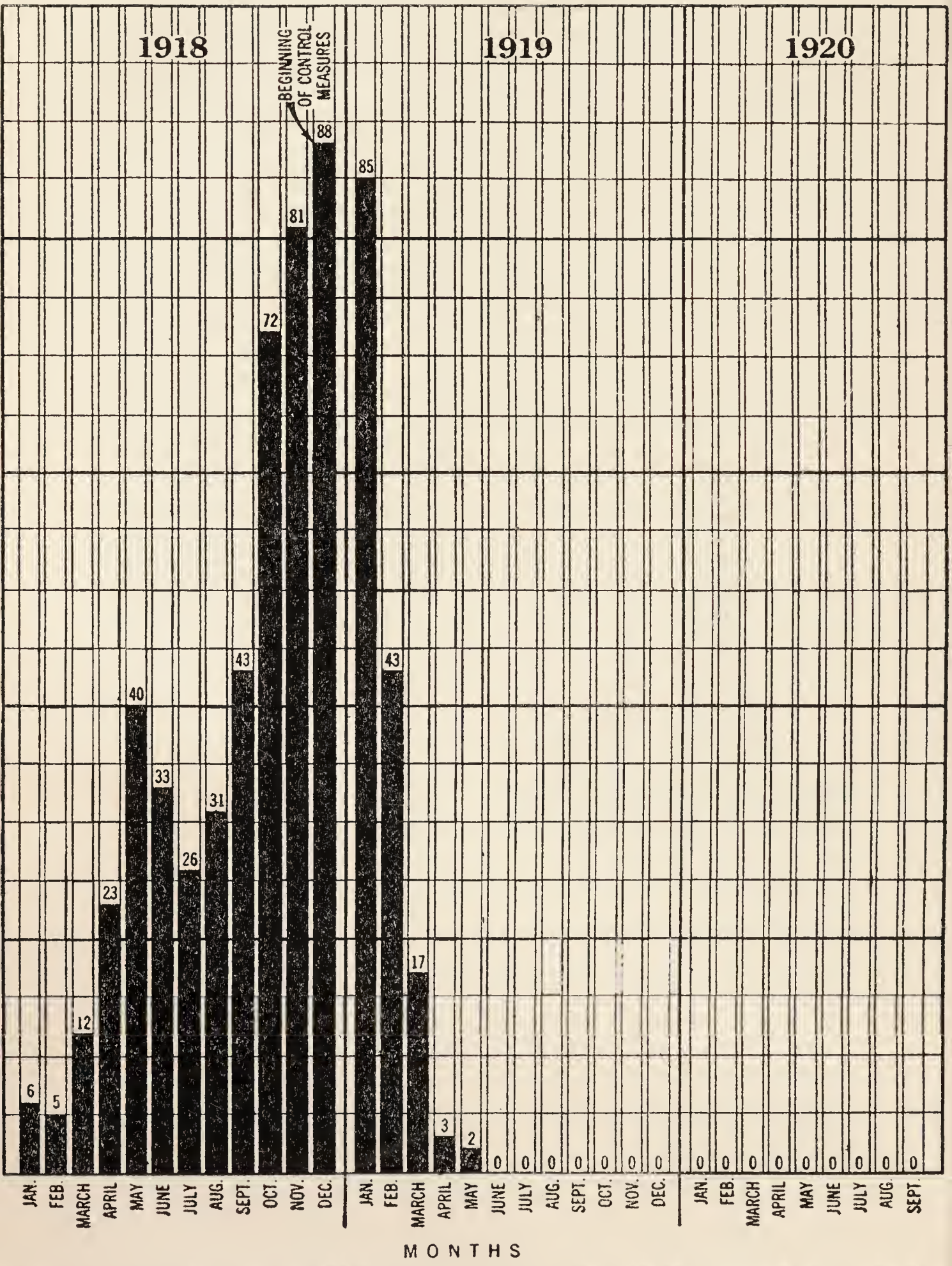


FIG. 58.—Disappearance of yellow fever from Guayaquil, Ecuador, as a result of control measures. (By permission of International Health Board).

born, than was formerly the case. It is furthermore plain that if nothing happens to the birth-rate there must eventually be as many persons living upon the habitable parts of the globe as can possibly be supported with food and the other necessities of life. Malthus, whom every one discusses but few take the trouble to read, pointed out many years ago that the problem of population transcends, in its direct importance to the welfare of human beings and forms of social organization, all other problems. Lately we have had a demonstration on a ghastly gigantic scale of the truth of Malthus' contention. For, in last analysis, it cannot be doubted that one important underlying cause of the great war, through which we have just passed, was the ever-growing pressure of population upon subsistence.

Any system or form of activity which tends, by however slight an amount, to keep more people alive at a given instant of time than would otherwise remain alive, adds to the difficulty of the problem of population. We have just seen that this is precisely what our public-health activities aim to do, and in which they succeed in a not inconsiderable degree. But someone will say at once that, while it is true that the death-rate is falling more or less generally, still the birth-rate is falling concomitantly, so we need not worry about the population problem. It is evident that if we regard the population problem in terms of world-area, rather than that of any particular country, its degree of immediacy depends upon the ratio of births to deaths in any given time unit. If we examine, as I have recently done, these death-birth ratios for different countries, we find that they give us little hope of any solution of the problem of population

by virtue of a supposed general positive correlation between birth-rates and death-rates.

The relation of birth-rate and death-rate changes to population changes is a simple one and may be put this way. If, neglecting migration as we are justified in doing in the war period and in considering the world problem, in a given time unit the percentage

$$\frac{\text{100 Deaths}}{\text{Births}}$$

has a value less than 100, it means that the births exceed the deaths and that the population is increasing within the specified time unit. If, on the other hand, the percentage is greater than 100, it means that the deaths are more frequent than the births and that the population is decreasing, again within the specified time unit. The

TABLE 29

Percentage of Deaths to Births

Year	77 non-invaded departments of France	Prussia	Bavaria	England and Wales
1913	97 per cent.	.....	58 per cent.	57 per cent.
1914	110 per cent.	66 per cent.	74 per cent.	59 per cent.
1915	169 per cent.	101 per cent.	98 per cent.	69 per cent.
1916	193 per cent.	117 per cent.	131 per cent.	65 per cent.
1917	179 per cent.	140 per cent.	127 per cent.	75 per cent.
1918	198 per cent.	132* per cent.	146 per cent.	92 per cent.
1919	154 per cent.	.....	.....	73 per cent.
1920	.....	.....	.....	42* per cent.

* First three-fourths of year only.

ratio of deaths to births may be conveniently designated as the vital index of a population.

From the raw data of births and deaths, I have calculated the percentage which the deaths were of the births for (a) the 77 non-invaded departments of France; (b)

Prussia; (c) Bavaria; and (d) England and Wales, from 1913 to 1920 by years. The results are shown in Table 29.

The points to be especially noted in Table 29 are:

1. In all the countries here dealt with the death-birth ratio in general rose throughout the war period. This means that the proportion of deaths to births increased so long as the war continued.

2. But in England it never rose to the 100 per cent. mark. In other words, in spite of all the dreadful effects of war, England's population went on making a net increase throughout the war.

3. Immediately after the war was over, the death-birth ratio began to drop rapidly in all countries. In England in 1919 it had dropped back from the high figure of 92 per cent. in 1918 to 73 per cent. In France it dropped from the high figure of 198 in 1918 to 154 in 1919, a lower figure than France had shown since 1914. In all the countries the same change is occurring at a rapid pace.

Perhaps the most striking possible illustration of this is the history of the death-birth ratio of the city of Vienna, shown in Figure 4, with data from the United States and England and Wales for comparison. Probably no single large city in the world was so hard hit by the war as Vienna. Yet observe what has happened to its death-birth ratio. Note how sharp is the decline in 1919 after the peak in 1918. In other words, we see how promptly the growth of population tends to regulate itself back towards the normal after even so disturbing an upset as a great war.

In the United States, the death-birth ratio was not affected at all by the war, though it was markedly altered by the influenza epidemic. The facts are shown in Figure 59 for the only years for which data are available.

The area covered is the United States birth registration area. We see that with the very low death-birth ratio of 56 in 1915, there was no significant change till the influenza year 1918, when the ratio rose to 73 per cent.

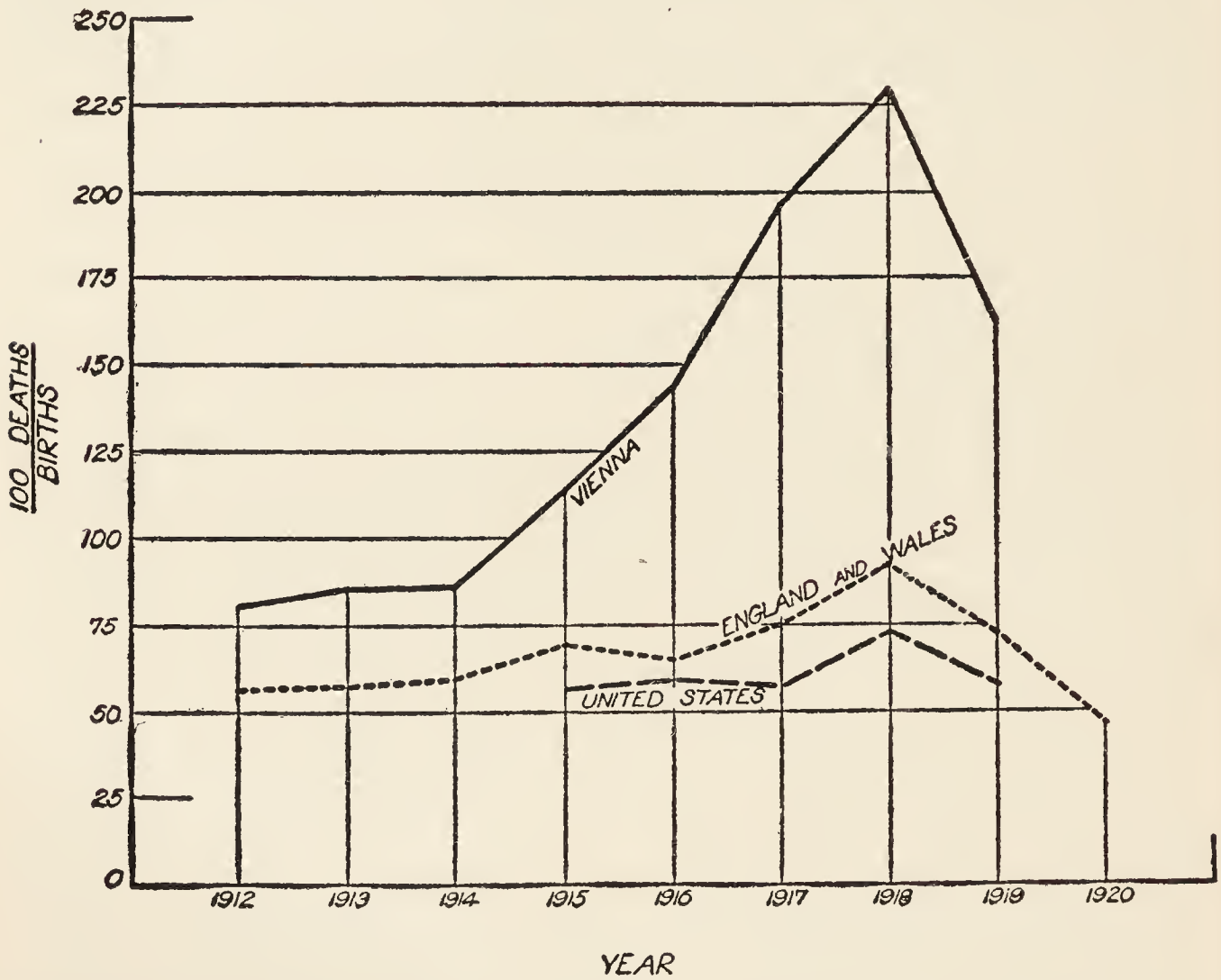


FIG. 59.—Showing the change in percentage which deaths were of births in each of the years 1912 to 1919 for Vienna (————); 1915 to 1919 for the United States (— — —); and 1912 to 1920 for England and Wales(------).

But in 1919, it promptly dropped back to the normal value of 57.98, almost identical with the 1917 figure of 57.34.

In England and Wales, the provisional figure indicates that 1920 will show a lower value for the vital index than that country has had for many years.

So we see that neither a highly destructive war, nor the most destructive epidemic since the Middle Ages, serves more than to cause a momentary hesitation in the steady onward march of population growth.

The first thing obviously needed in any scientific approach to the problem of population is a proper mathematical determination and expression of the law of population growth. It has been seen that the most devastating calamities make but a momentary flicker in the steady progress of the curve. Furthermore, population growth is plainly a biological matter. It depends upon, in last analysis, only the basic biological phenomena of fertility and mortality. To the problem of an adequate mathematical expression of the normal growth of populations, my colleague, Dr. Lowell J. Reed, and I have addressed ourselves for some time past. The known data upon which we have to operate are the population counts given by successive censuses. Various attempts have been made in the past to get a mathematical representation of these in order to predict successfully future populations, and to get estimates of the population in inter-censal years. A noteworthy attempt of this sort is Pritchett's fitting of a parabola of the third order to the United States population from 1790 to 1880 inclusive. This gave a fairly good result over the period, but was obviously purely empirical, expressed no real biological law of change, and in fact failed badly in prediction after 1890.

We have approached the problem from an *a priori* basis, set up a hypothesis as to the more important biological factors involved, and tested the resulting equation against the facts for a variety of countries. The hypothesis was built up around the following considerations:

1. In any given land area of fixed limits, as by political or natural boundaries, there must necessarily be an upper limit to the number of persons that can be supported on the area. To take an extreme case, it is obvious

that not so many as 25,000 persons could possibly stand upon an acre of ground, let alone live on it. So, similarly, there must be for any area an upper limiting number of persons who can possibly live upon it. In mathematical terms this means that the population curve must have an upper limiting asymptote.

2. At some time in the more or less remote past the population of human beings upon any given land area must have been nearly or quite zero. So the curve must have somewhere a lower limiting asymptote.

3. Between these two levels we assume that the *rate* of growth of the population, that is, the increase in numbers in any given time unit, is proportional to two things, namely:

a. The absolute amount of growth (or size of population) already attained;
b. The amount of as yet unutilized, or reserve, means or sources of subsistence still available in the area to support further population.

These hypotheses lead directly to a curve of the form shown in Figure 60, in which the position of the asymptotes and of the point of inflection, when the population is growing at the most rapid rate, are shown in terms of the constants. It is seen that the whole history of a population, as pictured by this curve, is something like this: In the early years following the settlement of a country the population growth is slow. Presently it begins to grow faster. After it passes the point where half the available resources of subsistence have been drawn upon and utilized, the rate of growth becomes slower, until finally the maximum population which the area will support is reached.

This theory* of population growth makes it possible to predict what the maximum population in a given area will be, and when it will be attained. Furthermore, one can tell exactly when the population is growing at the maximum rate. To test the theory, we have only to fit

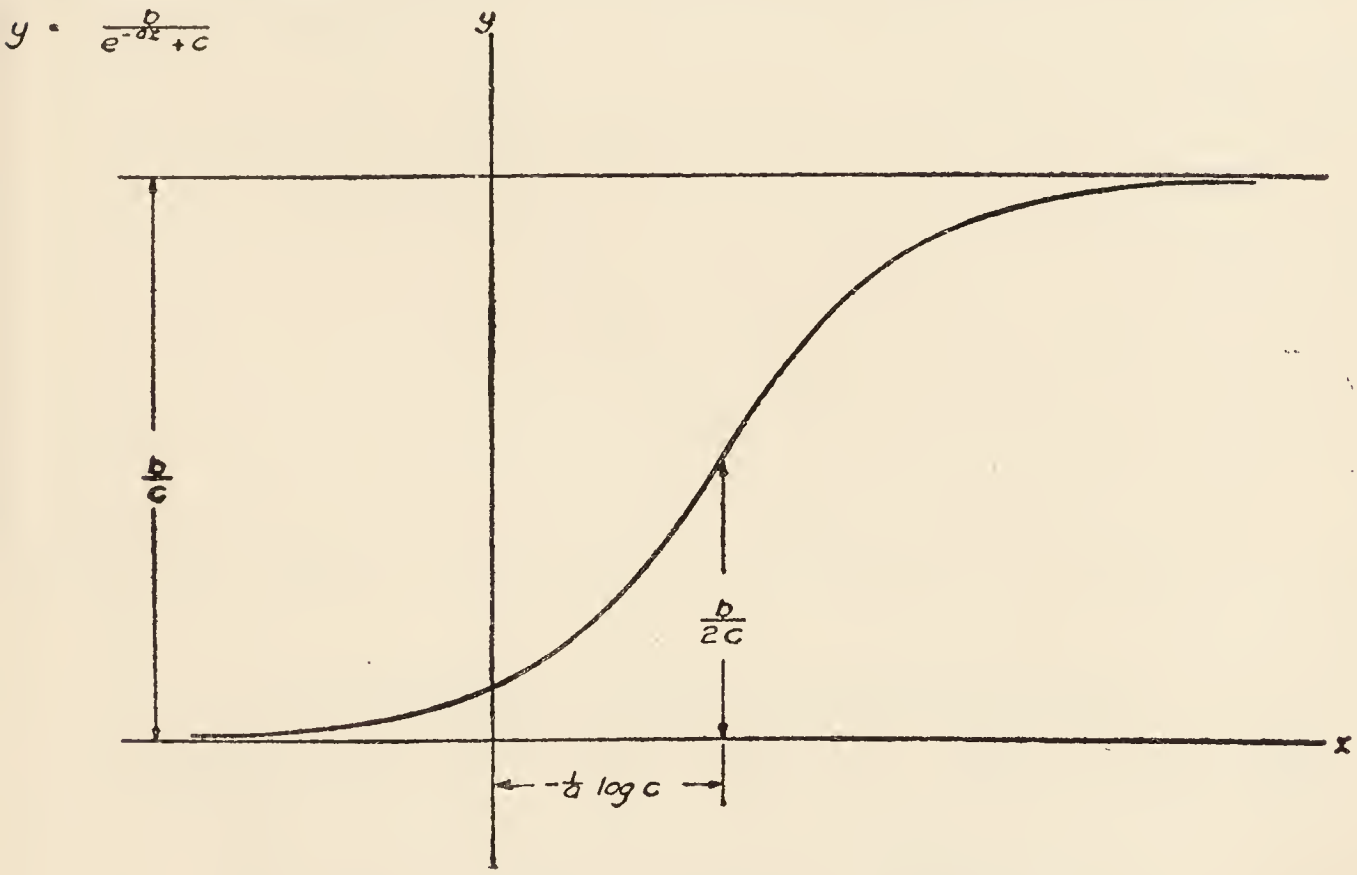


Fig. 60.—Showing a theoretical curve of population growth.

this theoretical curve to the known facts of population for any country by appropriate mathematical methods. If the hypothesis fits well all the known facts for a variety of countries in different stages of population growth, it may well be regarded as a first approximation to a substantially correct hypothesis and expressive of the biological law according to which population grows. In making this test the statistician has somewhat the same

* The mathematical hypothesis here dealt with is essentially the same as that of Verhulst, put forth in 1844. As Pearl and Reed pointed out in their first paper on the subject it is a special case of a much more general law. A comprehensive general treatment of the problem we are publishing shortly in another place. The generalization in no way alters the conclusions drawn here from a few illustrative examples.

kind of problem that confronts the astronomer calculating the complete orbit of a comet. The astronomer never has more than a relatively few observations of the posi-

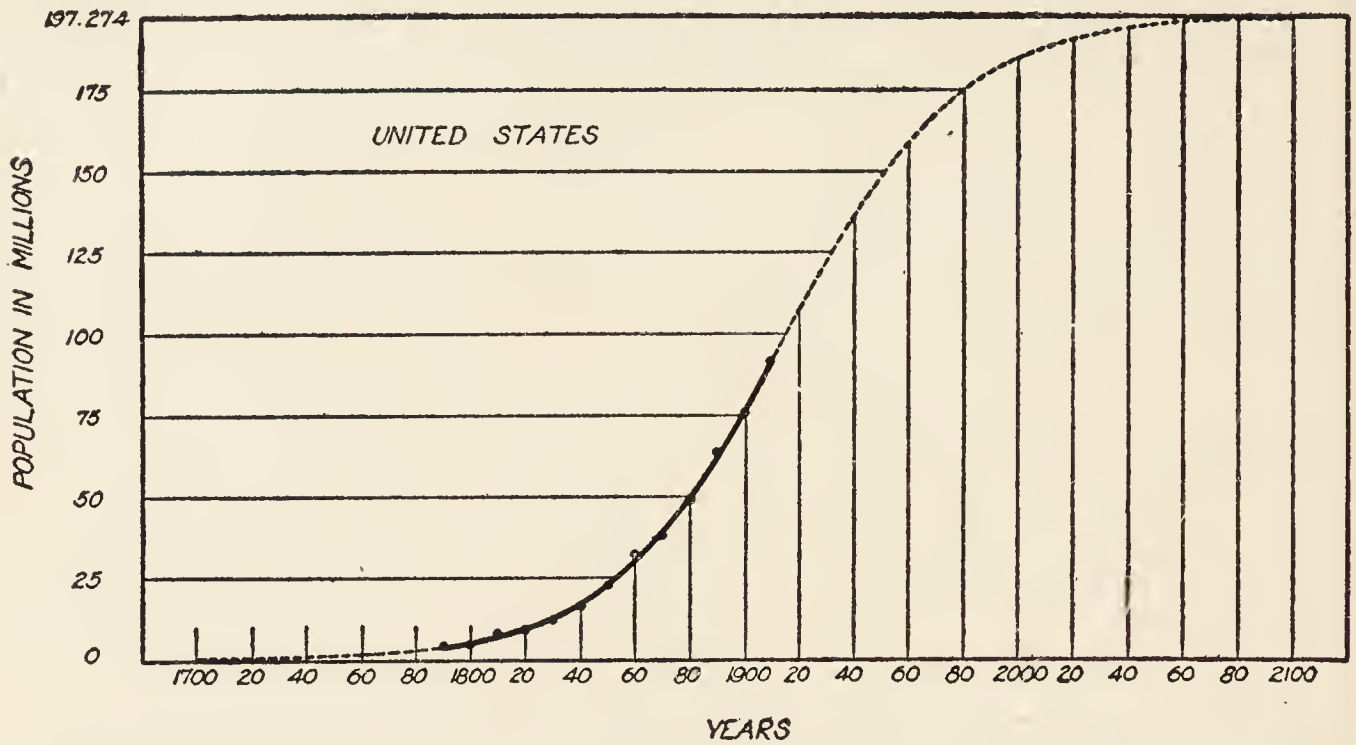


Fig. 61.—Showing the curve of growth of the population of the United States. For further explanation of this and the two following diagrams, see text.

tion of the comet. He has, from Newtonian principles, a general mathematical expression of the laws of motion of heavenly bodies. He must then construct his whole curve from the data given by the few observations. So, similarly, the statistician has but a relatively few population observations because census taking has been practised along present lines only a little more than a century. According to the stage in historical development of the country dealt with, he may have given an early, a late, or a middle short piece of the population "orbit" or history. From this he must construct, on the basis of his general theory of "population orbits," the whole history, past and future, of the population in question.

To demonstrate how successful the population curve shown in Figure 60 is in doing this, three diagrams are presented, each illustrating the growth of the population

in a different country. The heavy solid portion of each curve shows the region for which census data exist. The lighter broken part of the curve shows the portions outside this observed range. The circles show the actual, known observations. The first curve deals with the popu-

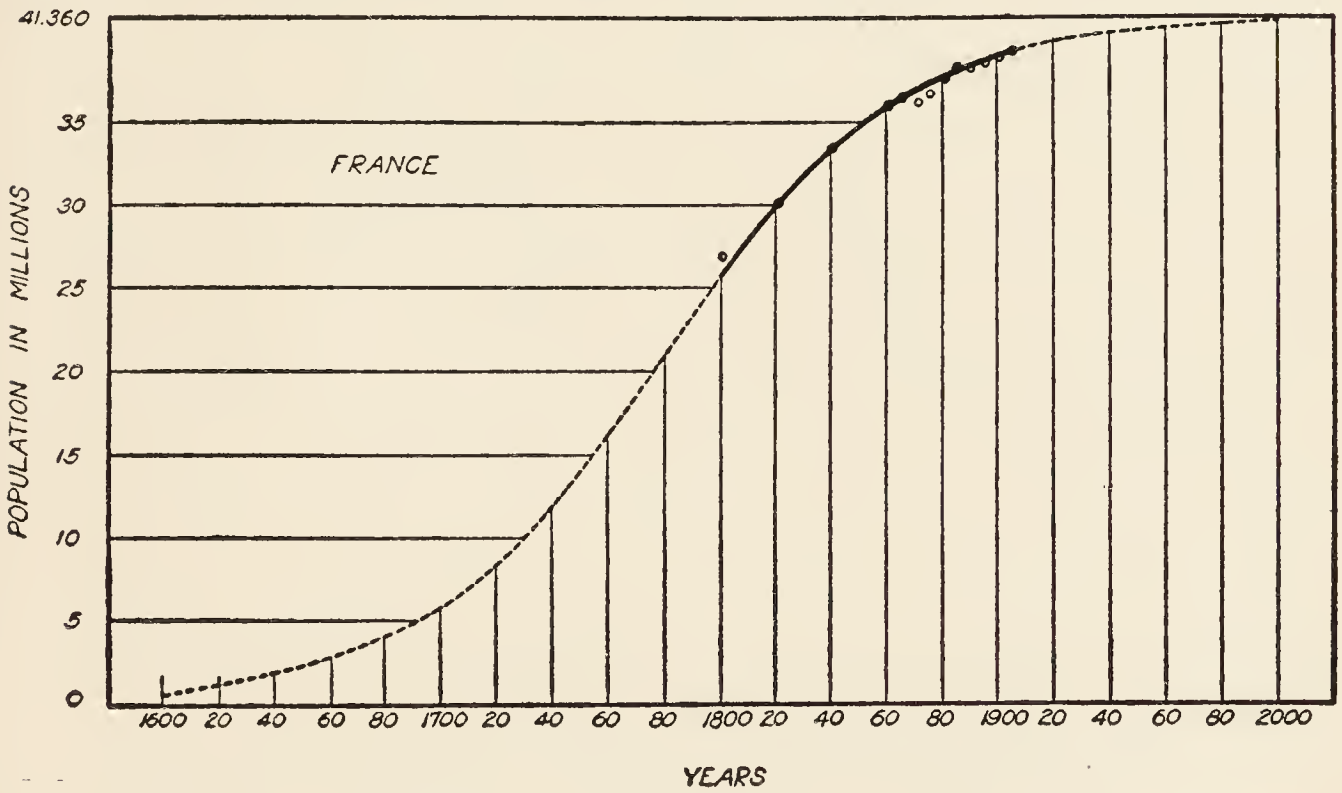


FIG. 62.—Showing the curve of growth of the population of France.

lation of the United States. Here the observations come from the first part of the curve, when the population was leaving the lower asymptote. First should be noted the extraordinary accuracy with which the mathematical theory describes the known facts. It would be extremely difficult, by any process, to draw a curve through the observed circles and come nearer to hitting them all than this one does.

Before considering the detailed consequences of this United States curve in relation to the whole population history of the country, let us first examine some curves for other countries, where the observed data fell in quite different portions of the "population orbit." Figure 62

gives the curve for France. Since before the time when definite census records began, France has been a rather densely populated country. All the data with which we had to work, belong therefore, towards the final end of the whole population history curve. The known population data for France and for the United States stand at opposite ends of the whole historical curve. One is an old country whose population is nearing the upper limit; the other a new country whose population started from near the lower asymptote only about a century and a half ago. But it is seen from the diagram that the general theory of population growth fits perfectly the known facts regarding France's population in the 120 years for which records exist. While there are some irregularities in the observation, due principally to the effects of the Franco-Prussian war, it is plain that on the whole it would be practically impossible to get a better fitting line through the observational circles than the present one.

We have seen that the general theory of population describes with equal accuracy the rate of growth in a young country, with rapidly increasing population, and an old country, where the population is approaching close to the absolute saturation point. Let us now see how it works for a country in an intermediate position in respect of population. Figure 63 shows the population history of Serbia. Here it will be noted at once that the heavy line, which denotes the region of known census data, lies about in the middle of the whole curve. Again the fit of theory to observation is extraordinarily close. No better fit, by a general law involving no more than 3 constants, could possibly be hoped for.

I think that these three examples, which could be multiplied to include practically every country for which

accurate population data exist, furnish a cogent demonstration of the essential soundness and accuracy of this theory of population growth. Indeed, the facts warrant, I believe, our regarding this as a first approximation to the true natural law of population growth. We now are

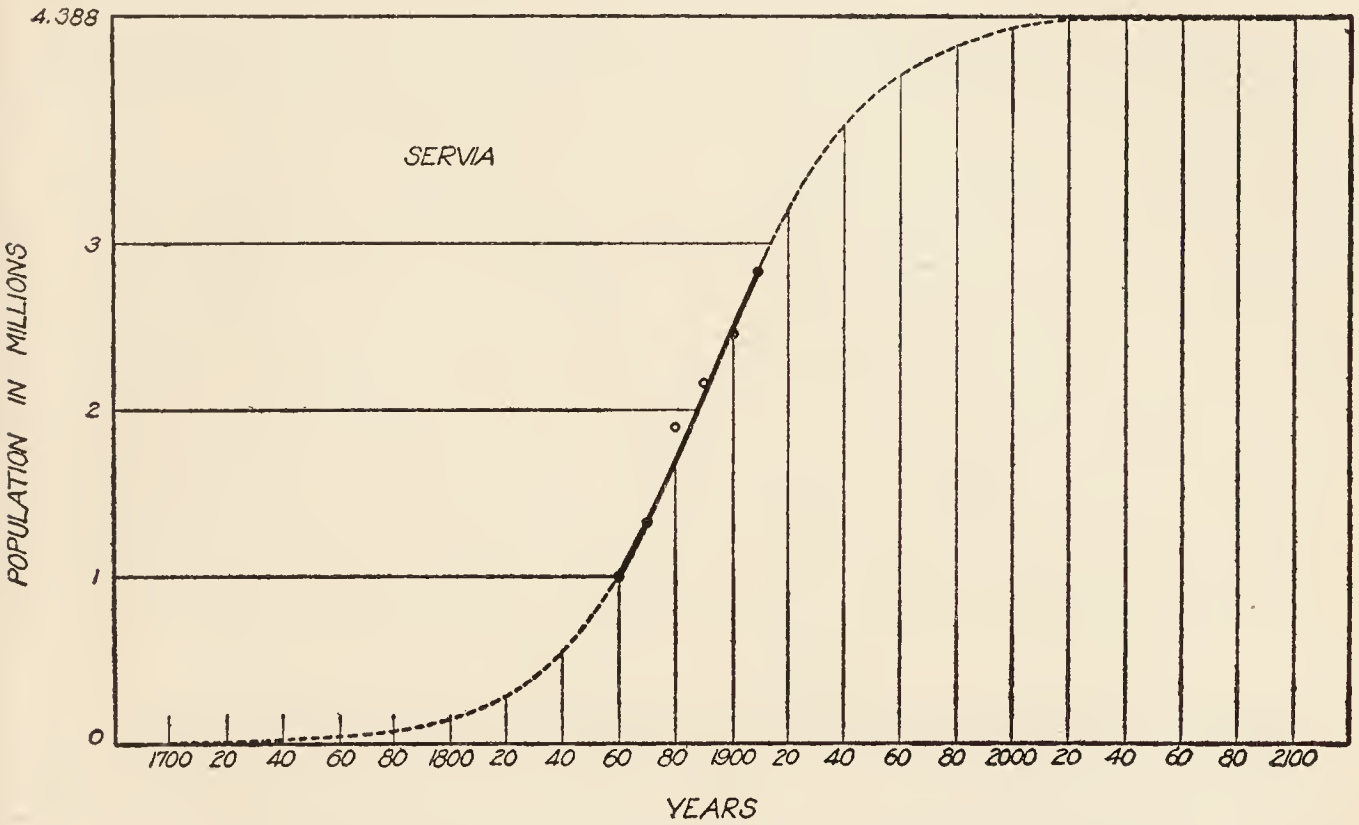


FIG. 63.—Showing the curve of growth of the population of Serbia.

approaching the proper mathematical foundation on which to build sociological discussions of the problem of population.

As a further demonstration of the soundness of this theory of population growth, let attention be directed for a moment to an example of its experimental verification. To a fruit fly (*Drosophila*) in a half pint milk bottle, such as is used in experimental work on these organisms, the interior of the bottle represents a definitely limited universe. How does the fly population grow in such a universe? We start a bottle with a male and female fly, and a small sample, say 10, of their offspring of different ages (larvæ and pupæ). The results are shown in Fig-

ure 64. The circles give the observed population growth, obtained by census counts at 3-day intervals. There can be no doubt that this population has grown in accordance with the equation. The two final observations lie below the curve, because of the difficulty experienced, in this

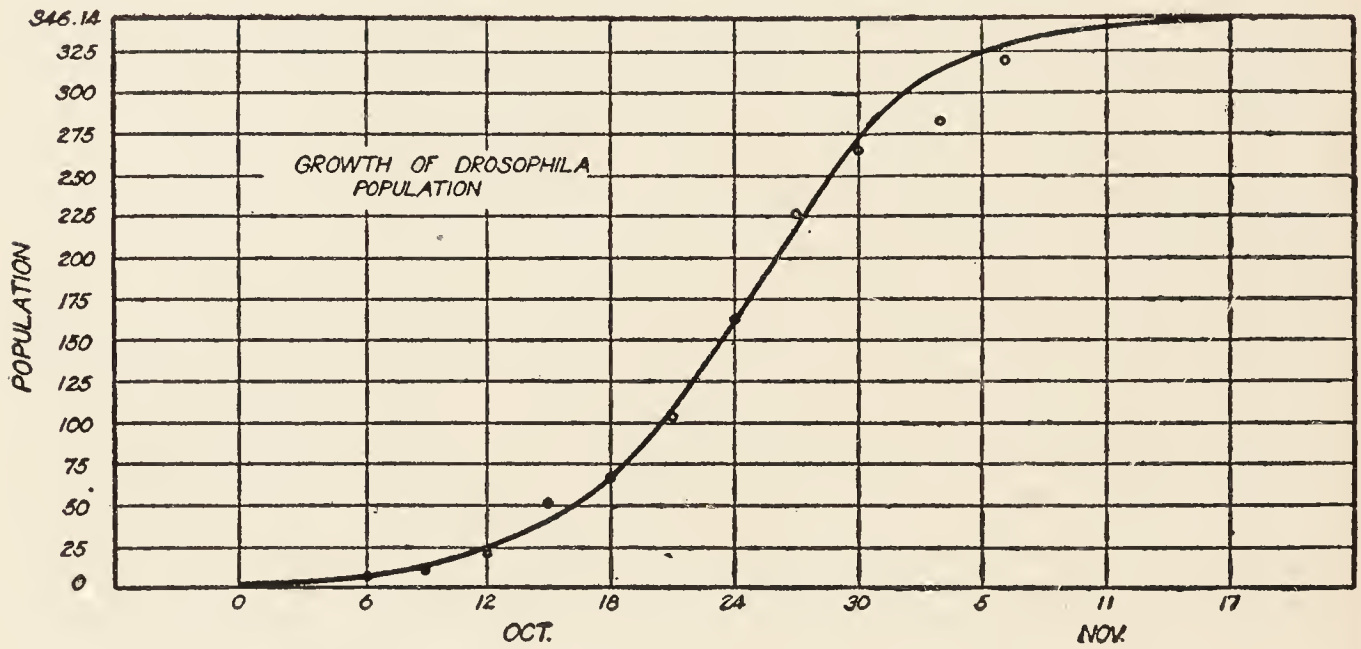


FIG. 64.—Showing the growth of a *Drosophila* population kept under controlled experimental conditions.

particular experiment, of keeping the food supply in good condition after so long a period from the start.

Let us return to the further discussion of the population problem of the United States in the light of the curve.

The first question which interests one is this: When did or will the population curve of this country pass the point of inflection and exhibit a progressively diminishing instead of increasing rate of growth? It is easily determined that this point occurred about April 1, 1914, on the assumption that our present numerical values reliably represent the rate of population growth in this country. In other words, so far as we may rely upon present numerical values, the United States has already passed its period of most rapid population growth, unless there

comes into play some factor not now known, and which has never operated during the past history of the country, to make the rate of growth more rapid. The latter contingency appears improbable. The 1920 census confirms the result, indicated by the curve, that the period of most rapid population growth was passed somewhere in the last decade. The population at the point of inflection works out to have been 98,637,000, which was, in fact, about the population of the country in 1914.

The upper asymptote given by the equation has the value of 197,274,000 roughly. This means that the maximum population which continental United States, as now areally limited, will have, will be roughly twice the present population; provided no fundamental new factor comes into play in the meantime, different in its magnitude and mode of operation from any of the factors which have influenced population growth in the past. This state of affairs will be reached in about the year 2,100, a little less than two centuries hence. Perhaps it may be thought that the magnitude of this number is not sufficiently imposing. It is so easy, and most writers on population have been so prone, to extrapolate population by geometric series or by a parabola or some such purely empirical curve, and arrive at stupendous figures, that calm consideration of real probabilities is most difficult to obtain. While we regard the numerical results as only a rough first approximation, it remains a fact that if anyone will soberly think of every city, every village, every town in this country having its present population multiplied by 2, and will further think of twice as many persons on the land in agricultural pursuits, he will be bound, we think, to conclude that the country would be

fairly densely populated. It would have about 66 persons per square mile of land area.

It will at once be pointed out that many European countries have a much greater density of population than 66 persons to the square mile, as, for example, Belgium with 673, the Netherlands with 499, etc. But it must not be forgotten that these countries are far from self-supporting in respect of physical means of subsistence. They are, or were before the war, economically self-supporting, which is a very different thing, because, by their industrial development at home and in their colonies, they produce money enough to buy physical means of subsistence from less densely populated portions of the world. We can, of course, do the same thing, provided that by the time our population gets so dense as to make it necessary, there still remain portions of the globe where food, clothing material and fuel are produced in excess of the needs of their home populations.

Now 197,000,000 people will require, on the basis of our present food habits, about 260,000,000 million calories per annum. The United States, during the seven years 1911-1918, produced as an annual average, in the form of human food, *both primary and secondary* (*i.e.*, broadly vegetable and animal), only 137,163,606 million calories per year. So that, unless our food habits radically change, and a man is able to do with less than 3,000 to 3,500 calories per day, or unless our agricultural production *radically* increases, which it appears not likely to do for a variety of reasons which cannot be here gone into, it will be necessary, when even our modest figure for the asymptotic population is reached, to import nearly or quite one-half of the calories necessary for that population. It seems improbable that the population will go on increasing at

any very rapid rate after such a condition is reached. East has shown that the United States has already entered upon the era of diminishing returns in agriculture in this country. Is it at all reasonable to suppose that by the time this country has closely approached the asymptote here indicated, with all the competition for means of subsistence which the already densely populated countries of Europe will then be putting up, there can be found any portion of the globe producing food in excess of its own needs to an extent to make it possible for us to find the calories we shall need to import?

Altogether we believe it will be the part of wisdom for anyone disposed to criticize our asymptotic value of a hundred and ninety-seven and a quarter millions because it is thought too small, to look further into all the relevant facts. This point of view is sustained in a recent paper by East in which the future agricultural resources of the country are particularly examined.

The relation of this already pressing problem of population to the problem of the duration of life is obvious enough. For every point that the death rate is lowered (or, what is the same thing, the average duration of life increased) the problem of population is made more immediate and more difficult unless there is a corresponding decrease in the birth-rate. Is it to be wondered at that most thoughtful students of the problem of population are advocates of birth control? Or is it remarkable that Major Leonard Darwin, president of the Eugenics Education Society in England, should say in a carefully considered memorandum to the new British Ministry of Health: "In the interests of posterity it is most desirable that parents should now limit the size of their families by any means held by them to be right (provided such

means are not injurious to health, nor, like abortion, an offense against public morals) to such an extent that the children could be brought up as efficient citizens and without deterioration in the standards of their civilization; and that parents should not limit the size of the family for any other reasons except on account of definite hereditary defects, or to secure an adequate interval between births.''

I am able to make no prediction as to how civilized countries will solve (if they do solve) the problems arising out of the impending saturation with human population of the portion of the earth's surface habitable by man. The certainty and assurance with which various ones of my friends advance solutions excites my wonder and admiration. But what impresses me even more is that scarcely any two of them agree on the nature of the panacea. To some it is birth control, to others synthetic foods derived from the atmosphere or elsewhere, and so on.

For myself, I am content if I have succeeded, in even a small measure, in indicating that population growth presents a problem fast becoming urgent; a problem that in its overwhelming significance and almost infinite ramifications touches upon virtually every present human activity and interest, and in particular upon the activities comprised in the terms public health and hygiene.

BIBLIOGRAPHY

The following list of literature in no sense aims at completeness within the field covered. It is, in the main, made up only of the sources which have been consulted in the preparation of the present volume. It is hoped, however, that even with this limitation it may serve as a useful introduction to the literature for any who may wish to pursue further their reading on the subjects here dealt with.

Amma, K. Über die Differenzierung der Keimbahnzellen bei den Kopepoden. *Arch. f. Zellforsch*, Bd. VI, 1911.

Bataillon. La parthenogenese experimentale des amphibiens. *Rev. gen. d. Sci.* T. XXII, p. 786, 1911. See also *Comp. rend. Acad. Sci.* Paris, T. CL, 996, 1910; T. CLII, 920, 1911; T. CLII, pp. 1120 and 1271, 1911; T. CLVI, 812, 1913; *Arch. de Zool. exper. et gen.*, T. XLVI, p. 103, 1910.

Beeton, M. and Pearson, K. Data for the problem of evolution in man. II.—A first study of the inheritance of longevity, and the selective death rate in man. *Proc. Roy. Soc.* Vol. LXV, pp, 290-305, 1899.

Beeton, M. and Pearson, K. On the inheritance of the duration of life, and on the intensity of natural selection in man. *Biometrika,* Vol. 1, pp. 50-89, 1901.

Bell, A G. The duration of life and conditions associated with longevity. A study of the Hyde genealogy. Washington, 1918. pp. 57, 4to. (Privately printed).

Benedict, Harris M. Senile changes in leaves of *Vitis vulpina L.* and certain other plants. *Cornell Agr. Expt. Stat.* Mem. 7, pp. 273-370, 1915.

Bertillon, J. Morbidity and mortality according to occupation. *Jour. Roy. Stat. Soc.*, Vol. LV, pp. 559-600, 1892.

Bogdanow, E. A. Über das Züchten der gewöhnlichen Fleischfliegen *(Calliphora vomitaria)* in sterilisierten Nahrmitteln. *Arch. f. d. ges. Physiol.* 1906

Bogdanow, E. A. Uber die Abhängigkeit des Wachstums der Fliegenlarven von Bakterien und Fermenten und über Variabilität und Vererbung bei den Fleischfliegen. *Arch. f. Anat. u. Physiol., (Physiol. Abth.)* 1908, pp. 173-199, 1908.

Bulloch, W. and Greenwood, M. The problem of tuberculosis considered from the standpoint of disposition. *Proc. Roy. Soc. Med.*, May, 1911, Vol. IV, Epidem. Sect., pp. 147-184.

Burrows, M. T. The tissue culture as a physiological method. *Trans. Cong. Amer. Phys. and Surg.*, Vol. IX, pp. 77-90, 4 plates, 1913.

Carrel, A. On the permanent life of tissues outside of the organism. *Jour. Exper. Med.* Vol. XV, pp. 516-528, 2 plates, 1912.

Carrel, A. Present condition of a strain of connective tissue twenty-eight months old. *Jour. Exper. Med.* Vol. XX, pp. 1-2, 2 plates, 1914.

Carrel, A. and Burrows, M. T. Cultivation of tissues *in vitro* and its technique. *Jour. Exper. Med.* Vol. XIII, pp. 387-396, 1911.

Carrel, A. and Ebeling, A. H. The multiplication of fibroblasts *in vitro*. *Jour. Exp. Med.* Vol. 34, pp. 317-337, 1921.

Carrel, A. and Ebeling, A. H. Age and multiplication of fibroblasts. *Ibid.* Vol. 34, pp. 599-623, 1921.

Child, C. M. Senescence and Rejuvenescence, Chicago, 1915, pp. 481.

Cohnheim, J. Vorlesungen über allgemeine Pathologie, 2te Aufl., Berlin, 1882.

Collis, E. L. and Greenwood, M. The Health of the Industrial Worker. London, 1921, 450 pp.

Conklin, E. G. The size of organisms and of their constituent parts in relation to longevity. senescence and rejuvenescence. *Pop. Sci. Mo.* August, 1913, pp. 178-198.

Crum, F. S. The effect of infant mortality on the after-lifetime of survivors. *Trans. 11th Ann. Meet. Amer. Child. Hyg. Ass.*, 1920, 17 pp.

Dawson, J. A. An experimental study of an amicronucleate *Oxytricha*. I.—Study of the normal animal, with an account of cannibalism. *Jour. Exp. Zool.* Vol. 29, pp. 473-512, 2 pl., 1919.

Dawson, M. M. Practical Lessons in Actuarial Science. 2 vols. New York, 1905.

Delage, Y. L'Hérédité et les grandes problèmes de la biologie. Paris, 1903.

Delcourt, A., and Guyénot, E. De la possibilité d'etudier certains Diptères en milieu défini *(Drosophila)*. *C.R. Ac. Sci.*, Paris, T.5, pp. 255-257, 1910.

Delcourt, A., and Guyénot, E. Variation et milieu. Lignées de Drosophiles en milieu stérile et défini. *C.R.* IV *Conf. Int. Gen.*, pp. 478-487, 1911.

Delcourt, A., and Guyénot, E. Génétique et milieu. Nécessité de la détermination des conditions; sa possibilité chez les Drosophiles. Technique. *Bull. Scient. France Belg.* T. XLV, pp. 249-333, 1911.

Doflein, Fr. Das Problem des Todes und der Unsterblichkeit bei den Pflanzen und Tieren. Jena, 1919.

Donaldson, H. H. The Growth of the Brain: a Study of the Nervous System in Relation to Education. London, 1895, 374 pp.

Dublin, L. I. A life table for the city of New Haven. *Amer. Publ. Health Jour.* Vol. VIII, pp. 580-581, 1918.

DUBLIN, L. I., with the collaboration of KOPF, E. W. and VAN BUREN, G. H. Mortality Statistics of Insured Wage-earners and their Families. New York, 1919, pp. viii and 397.

EAST, E. M. Population. *Sci. Monthly*, June 1920, pp. 603-624.

EAST, E. M. The agricultural limits of our population. *Ibid.* Vol. XII, June 1921, pp. 551-557.

EAST, E. M. and JONES, D. F. Inbreeding and Outbreeding. Their Genetic and Sociological Significance. Philadelphia, 1919, pp. 285. In the bibliography of this book will be found references to numerous papers by East and his students on heterosis in maize, etc.

EBELING, A. H. A strain of connective tissue seven years old. *Jour. Exper. Med.* Vol. XXX, pp. 531-537, 5 plates, 1919.

ENRIQUES, P. La morte. *Scientia.* T. I. 1907.

ENRIQUES, P. Duemila cinquecento generazione in un infusorio, senza conjugazione ne parthenogenesi, ne depressione. *Rend. della R. Accad. d. Sci. dell'Ist. di Bologna*, 1916, pp. (of reprint) 12.

ERDMANN, R. and WOODRUFF, L. L. The periodic reorganization process in *Paramecium caudatum*. *Jour. Exper. Zool.* Vol. 20, pp. 59-97, 1916.

FISHER, ARNE. On the construction of mortality tables by means of compound frequency curves. *Scandinavian Insurance Magazine*, 1920, *passim.*

FORSYTH, C. H. Vital and monetary losses in the United States due to preventable deaths. *Quart. Publ. Amer. Stat. Assoc.* Vol. 14, pp. 758-789, 1915.

FRIEDENTHAL, H. Über die Giltigkeit der Massenwirkung für den Energieumsatz der lebendigen Substanz. II Teil. *Zentralbl. f. Physiol.* Bd. 24, pp. 321-327, 1910.

GIVEN, D. H. C. Some deductions from the statistics on the prevention of pulmonary tuberculosis. *British Med. Jour.*, Feb. 12, 1921, p. 225.

GLOVER, J. W. United States Life Tables, 1910. Bureau of the Census, 1916, pp. 65.

GREENWOOD, M. Infant mortality and its administrative control. *Eugenics Rev.* October, 1912, pp. (of reprint) 1-23.

GREENWOOD, M. and BROWN, J. W. An examination of some factors influencing the rate of infant mortality. *Jour. Hyg.* Vol. XII, pp. 5-45, 1912.

GROTH und HAHN. Die Saüglingsverhältnisse in Bayern. München (Lindauer) *Sonderabdr. a.d. Ztschr. d.k. Bayer. Stat. Landesamts. Jahrg.* 1910.

GURNEY, J. H. The Comparative Ages to which Birds Live. *Ibis*, 1899, p. 19.

GUYÉNOT, E. Recherches sur la vie aseptique et la developpement d'un organisme en fonction du milieu. *Thesis*, Paris, 330 pp., 4 plates.

GUYER, M. E. The development of unfertilized frog eggs injected with blood. *Science*, N.S. Vol. XXV, p. 910, 1907.

HALLEY, EDM. An estimate of the degrees of mortality of mankind drawn from tables of births and burials in the city of Breslau, with an attempt to ascertain the price of annuities on lives. *Phil. Trans.* No. 196, p. 596.

HALLEY, EDM. Some further considerations on the Breslau bills of mortality. *Ibid.* No. 198, p. 654.

(Both of the above papers are reprinted in adequate abstract form in *Mem. Roy. Soc.* By Mr. M. Baddam, Vol. III, pp. 34-43; and pp. 52-53, 1739).

HARPER, M. Zur Entwicklung der Geschlechtsorgane von *Chironomus. Zool. Jahrbuch.; Abth. f. Anat. u. Ont.* Bd. XXXI, 1911.

HARRISON, R. G. The outgrowth of the nerve fiber as a mode of protoplasmic movement. *Jour. Exper. Zool.* Vol. IX, pp. 787-846, 1910.

HARRISON, R. G. The life of tissues outside the organism from the embryological standpoint. *Trans. Cong. Amer. Phys. and Surg.* Vol. IX, pp. 63-76, 12 plates, 1913.

HARTMANN, M. Uber die dauernde rein agame Züchtung von *Eudorina elegans* und ihre Bedeutung für das Befruchtungs—und Todproblem. *Sitz.-Ber. d.kgl. Akad. d. Wiss.* Berlin, Bd. 52, 1917.

HEGNER, R. W. The origin and Early History of the Germ Cells in Some Chrysomelid Beetles, *Jour. of Morphol.*, XX, 1909.

HEGNER, R. W. Experiments with Chrysomelid Beetles: III, The Effects of Killing Parts of the Eggs of *Leptinotarsa decemlineata. Biol. Bull.* XX, 1911.

HEGNER, R W. The History of the Germ Cells in the Pædogenetic Larvæ of *Miastor. Science* XXXVI. 1912.

HEGNER, R. W. Studies on Germ Cells: I, The History of the Germ Cells in Insects with Special Reference to the *Keimbahn-Determinants;* II, The Origin and Significance of the *Keimbahn-Determinants* in Animals." *Jour. of Morphol.*, XXV. 1914.

HEGNER, R. W. Studies on Germ Cells: III, The Origin of the Keimbahn-Determinants in a parasitic Hymenopteron, *Copidosoma. Anat. Anz.*, XLVI. 1914.

HEGNER, R. W. The Germ-Cell Cycle in Animals. New York. 1914.

HENDERSON, R. Mortality Laws and Statistics. New York, 1915, pp. v and 111.

HERON, D. On the relation of fertility in man to social status, and on the changes in this relation that have taken place during the last fifty years. *Draper's Company Res. Mem.* I, pp. 1-22, 1906.

HERSCH, L. L'inégalite devant la mort d'apres les statistiques de la Ville de Paris. Effets de la situation sociale sur la mortalité. *Rev. d'Econ.* pol. Nr. 3 and 4, 1920, 54 pp.

HERTWIG, R. Ueber Korrelation von Zell- und Kerngrosse und ihre Bedeutung fur die geschlechtliche Differenzierung und die Teilung der Zelle. *Biol. Centralbl.* Bd. XXIII, 1903.

HERTWIG, R. Ueber neue Probleme der Zellenlehre. *Arch f. Zellforsch.* Bd. I. 1908.

HODGE, C. F. Changes in ganglion cells from birth to senile death. *Jour. Physiol.* Vol. XVII, 129, 1894.

HOWARD, W. T. Senescence and natural death. *Cleveland Med. Jour.* Vol. IX, pp. 730-751, 1910.

HYDE, R. R. Inheritance of the length of life in *Drosophila, ampelophila.* Rept. Indiana Acad. Sci. 1913, pp. 113-123.

JENNINGS, H. S. Behavior of the Lower Organisms. New York, 1906, 366 pp.

JENNINGS, H. S. Assortative mating, variability and inheritance of size, in the conjugation of *Paramecium. Jour. Exper. Zool.* Vol. XI, pp. 1-134, 1912.

JENNINGS, H. S. Age, death and conjugation in the light of work on lower organisms. *Pop. Sci. Monthly,* June, 1912.

JENNINGS, H. S. Life and Death, Heredity and Evolution in Unicellular Organisms. Boston, 1920, pp. 233.

JICKELI, C. F. Die Unvollkommenheit des Stoffwechsels. Berlin, 1902.

JOLLOS. Die Fortpflanzung der Infusorien und die potentielle Unsterblichkeit der Einzelligen. *Biol. Centralbl.,* 1916.

KASSOWITZ, M. Allgemeine Biologie. Wien, 1899.

KORSCHELT, E. Lebensdauer, Altern und Tod. *Zweite Aufl.* Jena, 1922, 307 pp., 8 vo.

LANKASTER, E. R. On comparative longevity in man and the lower animals. London, 1870.

LEGRAND, M. A. La longévité a travers les âges. Paris, 1911, pp. 307.

LEVASSEUR, E. The tables of mortality and survivorship. *Jour. Roy. Stat. Soc.* Vol. 50, pp. 547-569, 1887. (Translated from *Jour. Soc. Stat. de Paris,* March 1887).

LEWIS, M. R. and LEWIS, W. H. The cultivation of tissues in salt solution. *Jour. Amer. Med. Ass.,* Vol. LVI, p. 1795, 1911.

LEWIS, M. R. and LEWIS, W. H. The cultivation of tissues from chick embryos in solutions of NaCl, $CaCl_2$, KCl and $NaHCO_3$ *Anat Rec.* Vol. V, pp. 277-293, 1911.

LILLIE, F. R. Problems of Fertilization. Chicago, 1919, 278 pp.

LOEB, J. Artificial Parthenogenesis and Fertilization. Chicago, 1913.

LOEB, J. The simplest constituents required for growth and the completion of the life cycle in an insect *(Drosophila). Science,* N.S. Vol. XLI, pp. 169-170, 1915.

Loeb, J. The salts required for the development of insects. *Jour. Biol. Chem.* Vol. XXIII, pp. 431-434, 1915.

Loeb, J. The sex of parthenogenetic frogs. *Proc. Nat. Acad.* Vol. 2, pp. 313-317, 1916.

Loeb, J. Natural death and the duration of life. *Sci. Monthly,* Dec. 1919, pp. 578-585.

Loeb, J. and Lewis, W. H. On the prolongation of the life of the unfertilized egg of sea-urchins by potassium cyanide. *Amer. Jour. Physiol.* Vol. VI, pp. 305-317, 1902.

Loeb, J. and Northrop, J. H. Is there a temperature coefficient for the duration of life? *Proc. Nat. Acad. Sci.* Vol. II, pp. 456-457, 1916.

Loeb, J. and Northrop, J. H. Nutrition and evolution. Second Note. *Jour. Biol. Chem.* Vol. XXVII, pp. 309-312, 1916.

Loeb, J. and Northrop, J. H. What determines the duration of life in Metazoa? *Proc. Nat. Acad. Sci.* Vol. III, pp. 382-386, 1917.

Loeb, J. and Northrop, J. H. On the influence of food and temperature upon the duration of life. *Jour. Biol. Chem.* Vol. XXXII, pp. 103-121, 1917.

Loeb, Leo. Observations on the inoculability of tumors and on the endemic occurrence of cancer. *Internat. Clinics,* Vol. III, (17th ser.), pp. 115-130, 15 plates, 1907.

Loeb, Leo. Tumor growth and tissue growth. *Proc. Amer. Phil. Soc.* Vol. XLVII, pp. 1-12, 1908.

Loeb, Leo. Discussion in symposium "On the Development of Tissues *in Vitro.*" *Trans. Cong. Amer. Phys. and Surg.* Vol. IX, pp. 99-101, 1913.

Loeb, Leo. Germ cells and somatic cells *Amer. Nat.* Vol. XLIX, pp. 256-305, 1915.

Loeb, Leo. General problems and tendencies in cancer research. *Science,* N.S. Vol. LXIII, pp. 293-303, 1916.

Loeb, Leo. The scientific investigation of cancer. *Sci. Monthly,* Sept. 1916, pp. 209-226.

Loeb, Leo. Tissue growth and tumor growth. *Jour. Cancer Research,* Vol. 11, pp. 135-150, 1917.

Loeb, Leo. Transplantation and individuality. *Biol. Bulletin,* Vol. XL. pp. 143-180, 1921.

Macdonell, W. R. On the expectation of life in ancient Rome, and in the provinces of Hispania and Lusitania and Africa. *Biometrika,* Vol. IX, pp. 366-380, 1913.

Metchnikoff, E. The Prolongation of Life. New York, 1908, pp. 343.

Minot, C. S. Age, Growth and Death. New York, 1908, pp. 280.

Mitchell, P. C. On Longevity and Relative Viability in Mammals and

Birds; with a Note on the Theory of Longevity. *Proc. Zool. Soc.* Lond. 1911, pp. 425-548.

Montgomery, T. H. Analysis of Racial Descent in Animals. New York, 1906, 311 pp.

Montgomery, T. H. On reproduction, animal life cycles, and the biological unit. *Trans. Texas Acad. Sci.* Vol. IX, 1906.

Morgan, T. H. The Physical Basis of Heredity. Philadelphia, 305 pp. In the bibliography of this book will be found references to numerous papers of Morgan and his students on *Drosophila.*

Mühlmann, M. Ueber die Ursache des Alters. Wiesbaden, 1900.

Müller, L. R. Ueber die Altersschätzung bei Menschen. Berlin, 1922, 62 pp., 8 vo.

Nascher, I. A noted case of longevity—John Shell: Centenarian. *Amer. Med. N.S.* Vol. XV, pp. 151-157, 1920.

Northrop, J. H. The role of yeast in the nutrition of an insect *(Drosophila). Jour. Biol. Chem.* Vol. XXX, pp. 181-187, 1917.

Northrop, J. H. The effect of prolongation of the period of growth on the total duration of life. *Ibid.* Vol. XXXII, pp. 123-126, 1917.

Pearl, R. The movements and reactions of fresh-water planarians: a study in animal behavior. *Q. J. Micr. Sci.* Vol. 46, N.S., pp. 509-714, 1902.

Pearl, R. A biometrical study of conjugation in *Paramecium. Biometrika.* Vol. V, pp. 213-297, 1907.

Pearl, R. Recent studies on growth. *Amer. Nat.* Vol. XLIII, pp. 302-316, 1909.

Pearl, R. On the mean age at death of centenarians. *Proc. Nat. Acad. Sci.* Vol. 5, pp. 83-86, 1919.

Pearl, R. On the embryological basis of human mortality rates. *Proc. Nat. Acad. Sci.* Vol. V, pp. 593-598, 1919.

Pearl, R. Some landmarks in the history of vital statistics. *Quart. Publ. Amer. Stat. Ass.* 1920, pp. 221-223.

Pearl, R. The Nation's Food. A Statistical Study of a Physiological and Social Problem. Philadelphia, 1920, 274 pp.

Pearl, R. Certain evolutionary aspects of human mortality rates. *Amer. Nat.* Vol. LIV, pp. 5-44, 1920.

Pearl, R. The effect of the war on the chief factors of population change. *Science,* N.S. Vol. LI, pp. 553-556, 1920.

Pearl, R. A further note on war and population. *Ibid.* Vol. LIII, pp 120-121, 1921.

Pearl, R. A biological classification of the causes of death. *Metron,* Vol. I, No. 3, pp. 92-99, 1921.

Pearl, R. The vitality of the peoples of America. *Amer. Jour. Hygiene,* Vol. I, pp. 592-674, 1921.

Pearl R. and Reed, L. J. On the rate of growth of the population of the United States since 1790 and its mathematical representation. *Proc. Nat. Acad. Sci.* Vol. VI, pp. 275-288, 1920.

Pearson, K. Mathematical contributions to the theory of evolution. II. Skew variations in homogeneous material. *Phil. Trans. Roy. Soc.* Vol. CLXXXVI, Ser. A. pp. 343-414, 1895.

Pearson, K. The Chances of Death and other Studies in Evolution. 2 vols. London, 1897.

Pearson, K. The Grammar of Science, Second Edit. London 1900, pp. 22 and 23.

Pearson, K. On the change in expectation of life in man during a period of circa 2000 years. *Biometrika,* Vol. I, pp. 261-264, 1902.

Pearson, K. The Scope and Importance to the State of the Science of National Eugenics. Third Edit. London (Cambridge Univ. Press), 1911, pp. 45.

Pearson, K. The Groundwork of Eugenics. Second Edit. London (Cambridge Univ. Press), 1912, pp. 39.

Pearson, K. Nature and Nurture the Problem of the Future. Second Edit. London (Cambridge Univ. Press) 1913, pp. 31.

Pearson, K. The check in the fall in the phthisis death-rate since the discovery of the tubercle bacillus and the adoption of modern treatment. *Biometrika,* Vol. 12, pp. 374-376, 1919.

Ploetz, A. Lebensdauer der Eltern und Kindersterblichkeit. *Arch f. Rassen- und Gesell- Biol.* Bd. 6, pp. 33-43, 1909.

Pritchett, A. S. A formula for predicting the population of the United States. *Quart. Publ. Amer. Stat. Ass.* Vol. II, pp. 278-286, 1891.

Richards, H. A. A study of New England mortality. *Quart. Publ. Amer. Stat. Assoc.* Vol. II, pp. 636-646, 1909 (N S. No. 88).

Ritter, W. E. The need of a new English word to express relation in living nature. *Jour. Phil. Psych. and Sci. Meth.* Vol. 18, pp. 1-18 (of reprint), 1921.

Robertson, T. B. and Ray, L. A. Experimental Studies on Growth. XII. The influence of pituitary gland (anterior lobe) tissue, tethelin, egg lecithin and cholesterol upon the duration of life of the white mouse. *Jour. Biol. Chem.* Vol. XXXVII, 427-442, 1919.

Robertson, T. B. and Ray, L. A. Experimental Studies on Growth XV. On the growth of relatively long lived compared with that of relatively short lived animals. *Jour. Biol. Chem.* Vol. XLII, pp. 71-107, 1920.

Romeis, B. Zur Verjüngungshypothese Steinachs. *Münch. med. Wchnschr.* 1921, No. 20.

Rose, W. Field experiments in malaria control. *Jour. Amer. Med. Assoc.* Vol. 73, pp. 1414—1420, 1919.

RUBNER, MAX. Das Problem der Lebensdauer und seine Beziehungen zu Wachstum und Ernährung. München und Berlin, 1908, 208 pp.

SLONAKER, J. R. The normal activity of the albino rat from birth to natural death, and its rate of growth and the duration of life. *Jour. Animal Behavior*, Vol. II, pp. 20-42, 1912.

SLOTOPOLSKY, B. Zur Diskussion über die potentielle Unsterblichkeit der Einzelligen und über den Ursprung des Todes. *Zool. Anz.* Bd. LI, pp. 63-71, and 81-91, 1920.

SNOW, E. C. The Intensity of Natural Selection in Man. *Draper's Company Research Mem.*, Studies in National Deterioration, VII, pp. 1-43, 1911.

STEINACH, E. Verjüngung durch experimentelle Neubelebung der alternden Pubertätsdrüse. *Arch. f. Entw.-Mech.* Bd., XLVI, pp. 557-619, 1920.

STEVENSON, T. H. C. The incidence of mortality upon the rich and poor districts of Paris and London. *Jour. Roy. Stat. Soc.* Vol. 84, pp. 90-99, 1921.

VERHULST, P. F. Recherches mathématiques sur la loi d'accroissement de la population. *Mém. de l'Acad. roy. de Bruxelles*, T. XVIII, pp. 1-58, 1844.

VERHULST, P. F. Deuxième mémoire sur la loi d'accroissement de la population. *Ibid.* T. XX, pp. 1-52, 1846.

VERWORN, M. Die Biogenhypothese. Jena, 1903.

WALLER, A. D. and DECKER, G. de. The physiological cost of muscular work measured by the exhalation of carbon dioxide. *Brit. Med. Jour.* May 7, 1921, No. 3149, pp. 669-671.

WALWORTH, R. H. Genealogy of the Hyde Family. 1861.

WEDEKIND. Teilung und Tod bei den Einzelligen. *Zool. Anz.* Bd. XLVIII, p. 190.

WEISMANN, A. The Duration of Life. In Essays upon Heredity and Kindred Biological Problems. Oxford, 1891. pp. 5-66.

WILSON, H. V. On the behavior of the dissociated cells in hydroids, *Alcyonaria*, and *Asterias*. *Jour. Exper. Zool.* Vol. XI, pp. 281-338, 1911.

WOODRUFF, L. L. So-called conjugating and non-conjugating races of *Paramecium*. *Jour. Exper. Zool.* Vol. 16, pp. 237-240, 1914.

WOODRUFF, L. L. The problem of rejuvenescence in Protozoa. *Biochem. Bul.* Vol. 4, pp. 371-378, 1915.

WOODRUFF, L. L. Rhythms and endomixis in various races of *Paramecium aurelia*. *Biol. Bul.* Vol. 33, pp. 51-56, 1917.

WOODRUFF, L. L. The influence of general environmental conditions on the periodicity of endomixis in *Paramecium aurelia*. *Biol. Bul.* Vol. 33, pp. 437-462, 1917.

WOODRUFF, L. L. The present status of the long-continued pedigree culture of *Paramecium aurelia* at Yale University. *Proc. Nat. Acad. Sci.* Vol. 7, pp. 41-44, 1921.

WOODRUFF, L. L. Amicronucleate infusoria. *Proc. Soc. Exp. Biol. Med.* Vol. 18, pp. 28-29, 1921.

WOODRUFF, L. L. and ERDMANN, R. A normal periodic reorganization process without cell fusion in *Paramecium*. *Jour. Exper. Zool.* Vol. 17, pp. 425-518, 1914.

WOODS, F. A. Origin and migration of germ-cells in *Acanthias*. *Amer. Jour. Anat.* Vol. I, p. 307.

YOUNG, T. E. On Centenarians; and the Duration of the Human Race. London, 1905 (Reissue) pp. 147.

INDEX